Towards the Total Synthesis of the Cytotoxic *Neo*-Clerodane Salvileucalin B

A thesis submitted for the Degree of Doctor of Philosophy

of The Australian National University

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Für Opi

Declaration

I declare that, to the best of my knowledge, the material presented in this Thesis represents the result of original work carried out by me in the period 2009-2013 and has not been submitted for examination for any other degree. This Thesis is less than 100,000 words in length. Wherever possible, established methodologies have been acknowledged by citation of the original publications from which they derive.

N. Heinrich

Nora Henrina Heinrich

November 2013

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First of all, I would like to thank my supervisor Professor Martin Banwell for the support over the years, the helpful discussions, his patience and positive attitude. I very much enjoyed working in the Banwell group and while I didn't wake up with a smile every day I am grateful for having been given the opportunity to work in this group, learn many lessons along the way and come out as a better scientist and wiser person. Thank you, Martin.

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Thank you to Dr. Mark Ellison for giving me the opportunity to develop my teaching skills, and to Sian, Owen, Craig and Mel for making report and exam marking so much fun. And obviously I'm grateful to all students that I have taught in the past four years for helping me learn how to be a better teacher.

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Most importantly, I thank my family for supporting me in everything I do, for giving the best advice and help from halfway around the globe, and just for being so special. I am incredibly lucky to have you as my family.

Publications and Presentations

The following list details the publications and presentations that have resulted from the author's research work performed during her candidature for the Degree of Doctor of Philosophy.

Publications:[*]

1. "Probing for the Pharmacophore of the Cytotoxic Neoclerodane Salvileucalin B." Nora Heinrich, Martin G. Banwell, Anthony C. Willis, Ian A. Cade, Robert J. Capon and Xiao-Cong Huang *The Australian Journal of Chemistry*, **2012**, *65*, 1679-1686.

2. "Reversible Cyclopropane Ring-Cleavage Reactions within Etheno-Bridged [4.3.1]Propelladiene Frameworks Leading to Aza- and Oxa-[5.6.5.6]fenestratetraenes." Nora Heinrich, Anthony C. Willis, Ian A. Cade, Junming Ho, Michelle L. Coote and Martin G. Banwell *Chemistry—A European Journal*, **2012**, *18*, 13585-13588.

Presentations:

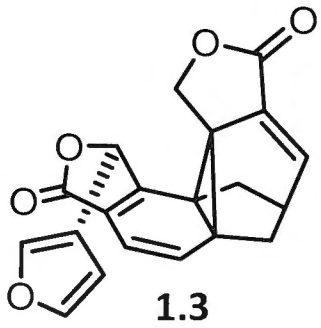
1. *"Towards the Total Synthesis of Salvileucalin B: Assembly of the Caged Core Structure."* Short talk at the RACI NSW Organic Chemistry Group One-Day Symposium, Wollongong, 1 December 2010.

2. "Opening and Closing a Chemical Window – Reversible Formation of Aza- and Oxa-[5.6.5.6]fenestranes". Poster presentation at the RACI NSW Organic Chemistry Group One-Day Symposium, Sydney, 6 December 2012.

[*] Reprints of these publications are contained within Appendix 11.

Abstract

The work described in this Thesis was directed towards establishing a total synthesis of the cyclopropane-containing natural product salvileucalin B (**1.3**). The initial focus was the formation of its caged core and propellane-containing substructure as embodied in lactone **1.13**. This incorporates an α-methylene-γ-butyrolactone-type subunit thought to be contributing to the biological properties of the natural product. The protecting group free synthesis of compound **1.13** was eventually achieved using an intramolecular Büchner reaction as the key step. Elaboration of the [4.3.1]propellane **2.37** formed as a result of this process engaged in unusual and reversible rearrangement reactions leading to various novel fenestranes. The enantioselective desymmetrisation of *meso*-compound **1.13** was achieved through Kornblum-DeLaMare rearrangement of the derived *endo*-peroxide, thus providing the means by which an enantioselective total synthesis of target **1.13** could eventually be realised.



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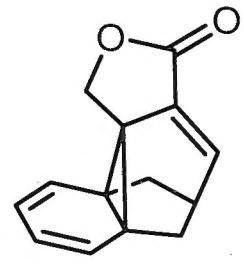

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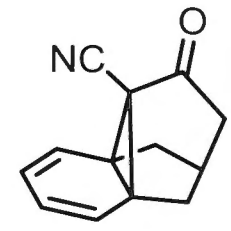
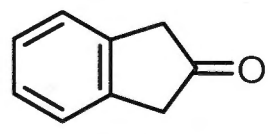


2.37

Chapter One provides a brief introduction to the most important compounds isolated from plants of the *Salvia* genus, including the title compound **1.3**. This is followed by a discussion of previous efforts directed towards its synthesis.

Chapter Two details the synthetic work carried out by the author in seeking to prepare lactone **1.13**. The original approach, involving a dibromocarbene addition reaction to establish the [4.3.1]propellane framework, was eventually replaced by an intramolecular Büchner reaction that exploited the rhodium-catalysed decomposition of diazoketone **2.34** for this purpose. Both approaches used indan-2-one **2.7** as the starting material. Once the target core lactone **1.13** was successfully synthesised, it was subjected to hydrogenation reactions employing three different types of catalysts. In this way the partially and fully hydrogenated lactone analogues **2.77** - **2.82** were produced with three of these still containing the α-methylene-γ-butyrolactone-type subunit. These compounds and the core lactone **1.13** itself were each subjected to biological testing which revealed, rather surprisingly, that they were all essentially inactive.



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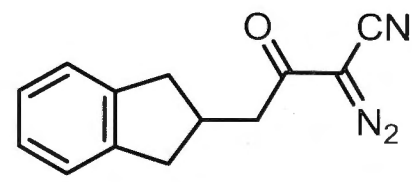

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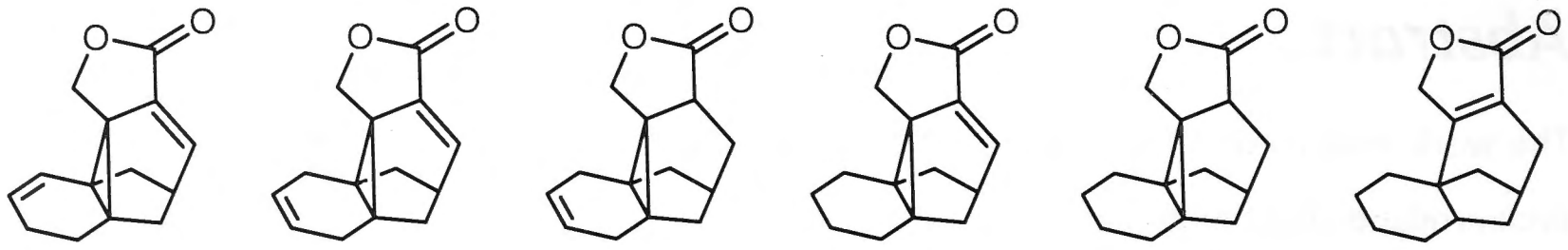
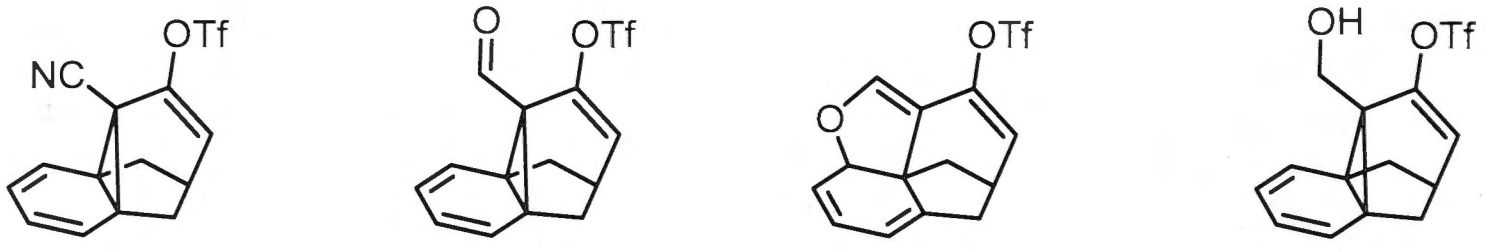


2.77 **2.78** **2.79** **2.80** **2.81** **2.82**

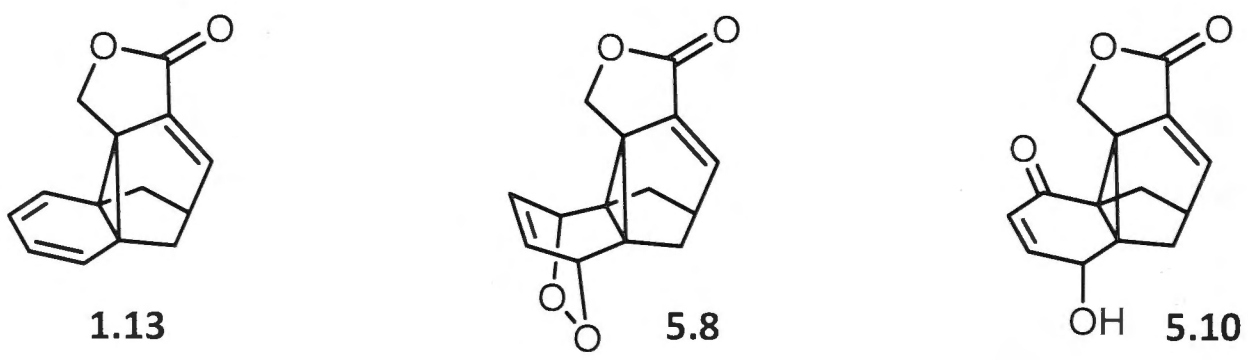
Chapter Three details investigations into a rearrangement that was discovered during the course of carrying out the DIBAL-H-mediated reduction of the nitrile group within compound **2.61** (a precursor to lactone **1.13**) and which led, unexpectedly and presumably *via* a [3,5]-sigmatropic rearrangement of aldehyde **2.62**, to the formation of oxa-[5.6.5.6]fenestratetraene **3.51**. Computational calculations support the notion that the conversion **2.62** → **3.51** is a direct one and doesn't involve a [3,3]-sigmatropic rearrangement followed by a 1,3-shift. Subjection of fenestrane **3.51** to a second DIBAL-H-mediated reduction yielded the symmetrical alcohol **2.63** and thus confirming the reversible nature of the proposed [3,5]-sigmatropic rearrangement process.



2.61 **2.62** **3.51** **2.63**

Chapter Four describes the investigation into the use of the Büchner reaction as a means for making various propellanes and fenestranes related to compounds **1.13** and **3.51**, respectively. However, such efforts were thwarted by a range of C-H insertion reactions that occurred instead of the desired intramolecular Büchner process.

The work reported in Chapter Five was concerned with the late-stage desymmetrisation of *meso*-core lactone **1.13**. Several desymmetrisation protocols were investigated with the enantioselective Kornblum-DeLaMare (KDLM) rearrangement of the derived *endo*-peroxide **5.8** being the most effective and resulting in formation of γ-hydroxyenone **5.10**. A possible synthetic route to salvileucalin B (**1.3**) based on such work is also presented.



1.13 **5.8** **5.10**

Glossary

The following abbreviations have been used throughout this thesis:

Å	Ångstrom
Ac	acetyl
acac	acetylacetonate
aq.	aqueous
$[\alpha]_D$	specific rotation (at the sodium D-line)
atm	atmosphere
t-Bu	*tertiary*-butyl
n-Bu	*normal*-butyl
ca.	*circa* (around)
cat.	catalytic
COSY	correlation spectroscopy
d	doublet
DCM	dichloromethane
DIBAL-H	di*iso*butylaluminium hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide
DMP	dimethoxypropane
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
E	*entgegen* (opposite)
e.g.	*exempli gratia* (for example)
EI	electron impact (mass spectrometry)
equiv.	equivalents
ESI	electrospray ionisation (mass spectrometry)
Et	ethyl
et al.	*et alia* (and others)
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
eV	electron Volt
FGI(s)	functional group interconversions(s)
g	gram(s)

GCMS	gas chromatography-mass spectrometry
gem	geminal
h	hour(s)
HCl	hydrochloric acid
HREIMS	high resolution electron-impact mass spectrometry
hv	irradiation with light
Hz	Hertz
i.e.	*id est* (that is)
IR	infrared
J	coupling constant (Hz)
Lg	leaving group (of unspecified form)
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molar
$M^{+\bullet}$	molecular ion
Me	methyl
MeOH	methanol
MHz	mega-Hertz
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
MS	mass spectrometry
m/z	mass-to-charge ratio
Nf	nonafluoromethanesulfonyl
NIS	*N*-iodosuccinimide
nm	nanometre(s)
NMR	nuclear magnetic resonance
o	*ortho*
org.	organic
ORTEP	Oak Ridge Thermal Ellipsoid Plot
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
PNB	*p*-nitrobenzoyl

ppm	parts per million
PS 30-40	petroleum spirits (boiling range 30-40 °C)
PTAD	4-phenyl-1,2,4-triazole-3,5-dione
q	quartet
quant.	quantitative
ref.	reference
R	unspecified alkyl group
R_f	retardation factor (in thin layer chromatography)
s	singlet
(s)	solid
sat.	saturated
t	triplet
TEBAC	triethylbenzylammonium chloride
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxy radical
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid/trifluoroacetate
THF	tetrahydrofuran
Ts	toluenesulfonyl
UV	ultra violet (spectroscopy)
viz.	namely (from Latin *videlicit*)
v/v	unit volume per unit volume (ratio)
Z	zusammen (together)
δ	chemical shift (parts per million)
°C	degrees Celsius
µg	microgram(s)
µL	microlitre(s)

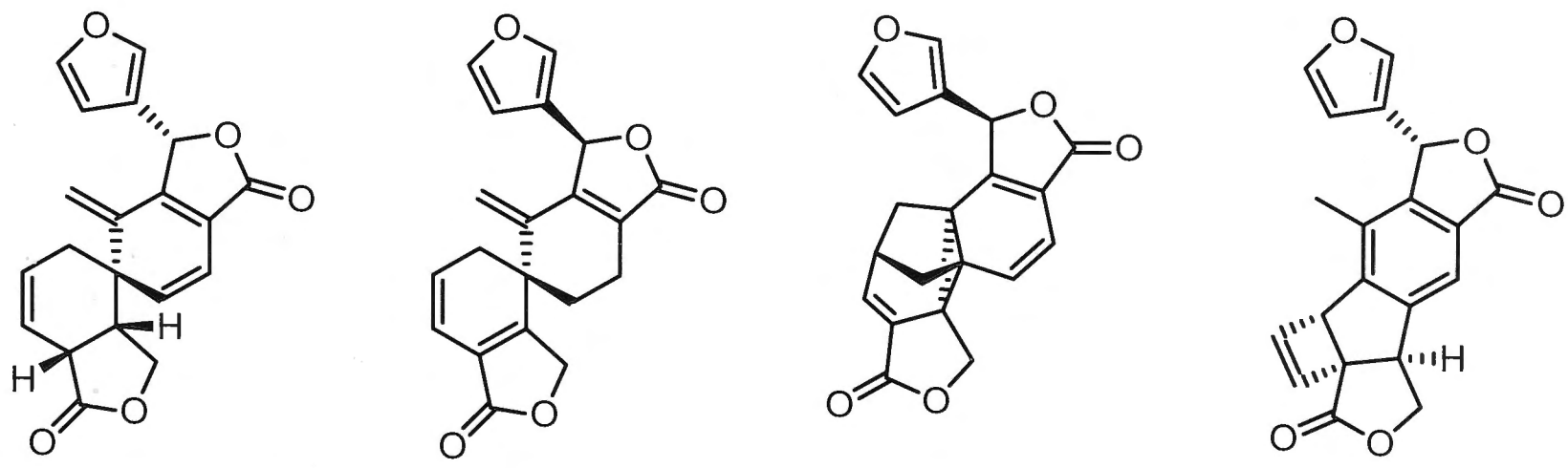
Table of Contents

Chapter 1

Salvileucalin B: A Structurally Interesting Neo-Clerodane Diterpenoid

1.1. Isolation and Structure of the *Salvia* Family of Diterpenoids

Several biologically active compounds were isolated from the aerial parts of the plant *Salvia leucantha*, (Mexican bush sage) of the subgenus Calosphace (family Labiatae) by Esquivel *et al*. in 1994[1] and then by Takeda *et al*. in 2006.[2] These included spiroleucantholide (**1.1**) which features an unusual spiro moiety (Figure 1.1). In follow-up studies reported by Takeya *et al.* in 2008[3] they reported the isolation of salvileucalins A (**1.2**) and B (**1.3**) from the aerial parts of the same plant. In 2011 the isolation and characterisation of salvileucalin C (**1.4**) was reported by the same group.[4] The structures of these compounds, including their absolute configurations, were determined using a combination of single-crystal X-ray analysis and vibrational circular dichroism (VCD).

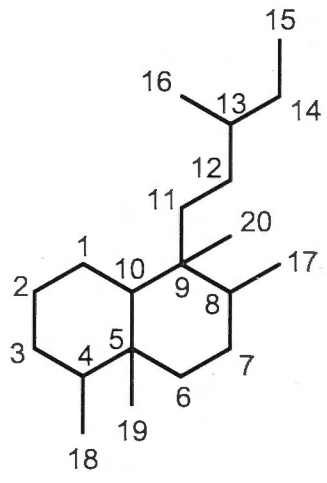


Spiroleucantholide **1.1** | Salvileucalin A **1.2** | Salvileucalin B **1.3** | Salvileucalin C **1.4**

Figure 1.1. Structurally relevant *neo*-clerodanes isolated from certain Salvia species of plants.

Most diterpenoids isolated from the *Salvia* species incorporate the clerodane framework (**1.5**) (Figure 1.2) or are rearranged derivatives thereof. More broadly speaking, diterpenoids incorporating the clerodane framework (**1.5**) are widely distributed in Nature with more than 100 such compounds having been isolated from the Labiatae family alone.[3]

The clerodane framework is defined by the presence of a decalin core embodying five contiguous stereocentres at C4, C5, C8, C9 and C10. Clerodane compounds that possess the same absolute stereochemistry as clerodin (**1.6**) (the first known member of the clerodane series) are defined as *neo*-clerodanes, while their enantiomers are called *ent-neo*-clerodanes.[5] As a member of the *neo*-clerodane class of compounds, salvileucalin B (**1.3**) has attracted particular interest because it is the first such diterpenoid to embody a caged-carbon framework.[3]



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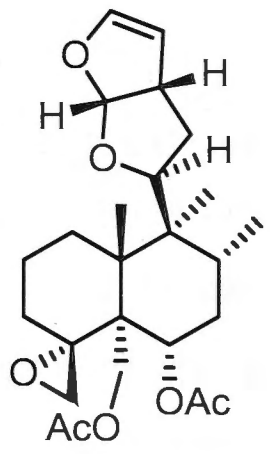


1.6

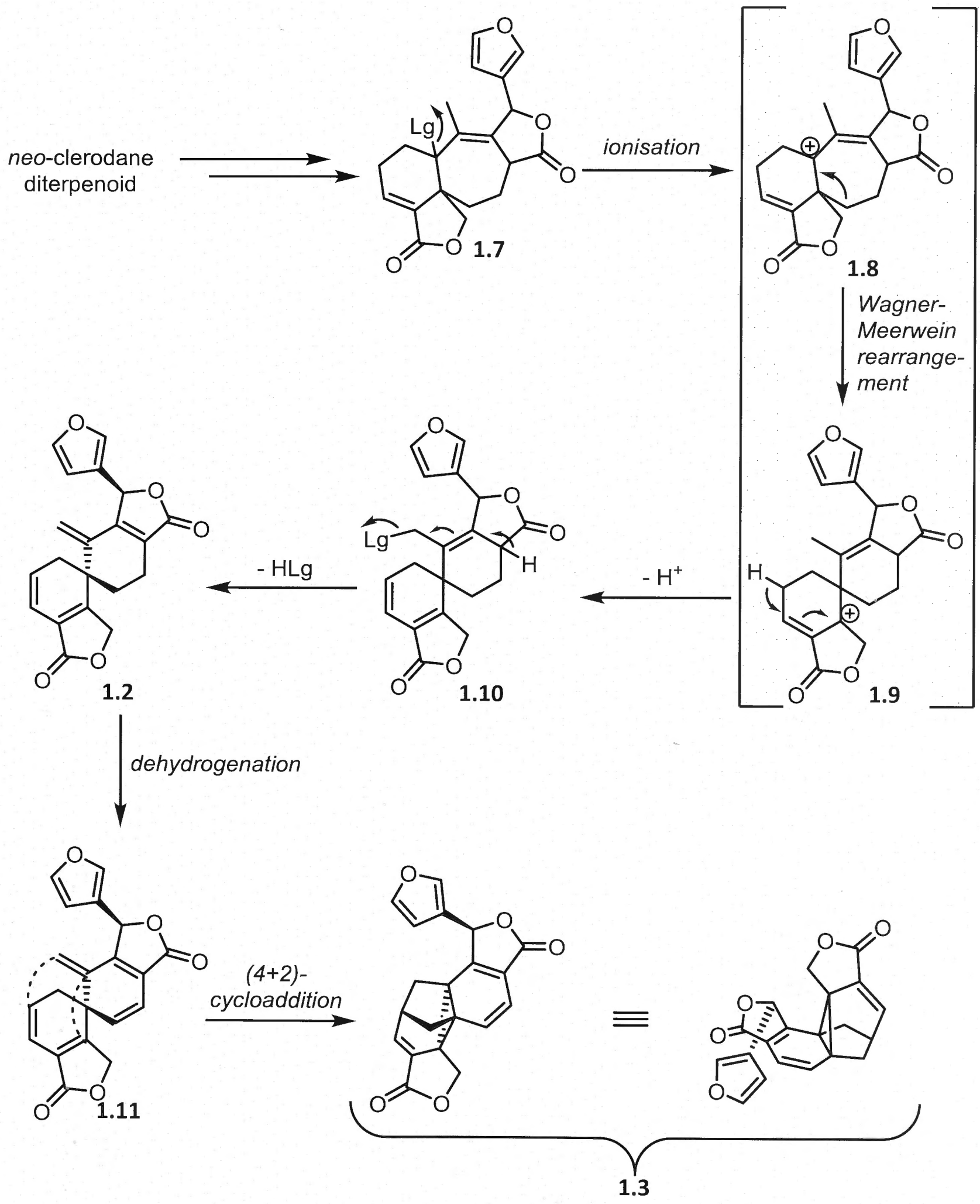
Figure 1.2. The clerodane framework (**1.5**) and the natural product clerodin (**1.6**).

Clerodanes often incorporate a lactone ring and an attached furan moiety, as is the case for all of the compounds shown in Figure 1.1. Although the degree of rearrangement of the decalin core and oxygen content may vary, the majority of clerodanes share common biosynthetic origins details of which are provided in the following section.

1.2. Proposed Biogenesis of Salvileucalin B

A possible biosynthetic pathway[3] leading to salvileucalin B (**1.3**) (Scheme 1.1) has been proposed by Takeya *et al*. Thus, it is suggested that compound **1.7**, which was "possibly derived from clerodane diterpenoids", could rearrange, *via* cation **1.8**, to form the spiro isomer **1.9**. Loss of a proton from cation **1.9** and elimination of the elements of HLg within the ensuing compound, **1.10**, would then lead to salvileucalin A (**1.2**). Although the existence of enzymes catalysing intramolecular Diels-Alder reactions[6] was controversial at the time of publication, it was suggested that the structurally novel propellane core of salvileucalin B (**1.3**) was formed through just such a process involving the triene moiety associated with compound **1.11**, a

dehydro-derivative of salvileucalin A (**1.2**). This proposal is supported by recent synthetic[7] and computational[8] studies.

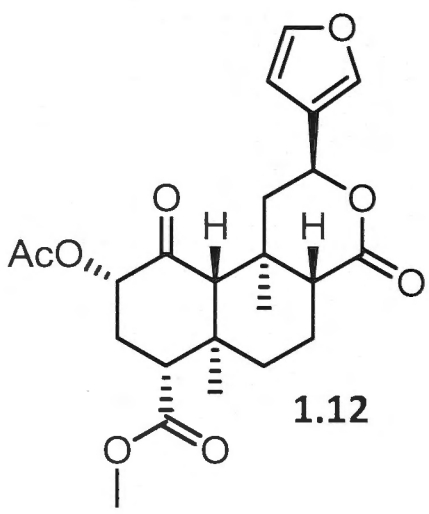


Scheme 1.1. Proposed biosynthetic pathway leading to the formation of salvileucalin B (**1.3**).

1.3. Biological Activities of Compounds Isolated from *Salvia* Species

Many *neo*-clerodane natural products are biologically active and are considered to have potential as antiviral, antitumor, antifungal, antibacterial, anti-peptic ulcer and/or psychotropic agents.[9] The most well-known member of the neo-clerodane class is salvinorin A (**1.12**) (Figure 1.3) which was isolated from *Salvia divinorum* (Family Labiatae) by Ortega *et al.* in 1982.[10] To date, it has received the most synthetic attention,[11] however, this has mostly been focused on its derivatisation and the testing of the biological activities of the compounds so formed. The first total synthesis of salvinorin A was not reported until 2007.[11c] Interestingly, this natural product is the only non-nitrogen-containing psychoactive substance. Indeed, it is the most potent naturally-occurring hallucinogen known.[11c]

Amongst the series of compounds isolated from *Salvia leucantha*, thus far only salvileucalin B (**1.3**) has been reported to have any biological activity. Specifically, it exerts cytotoxic activity against the A549 and HT-29 human adenocarcinoma cell lines with half maximal inhibitory concentration (IC_{50}) values of 15.7 and 5.6 mM, respectively.[3] These effects might well be attributed to the presence of the α-alkylidene-γ-butyrolactone-type moiety embedded within the polycyclic framework.[12] Accordingly, it could be argued[13] that the basic pharmacophore[14] associated with salvileucalin B (**1.3**) is embodied within the lactone-containing caged core substructure and that this, as well as related systems such as the caged core lactone **1.13**, should display similar activities to the natural product.



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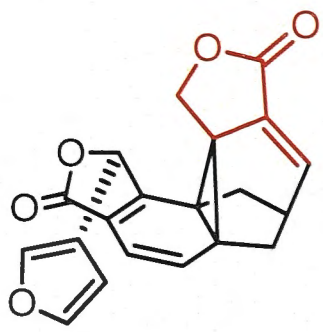

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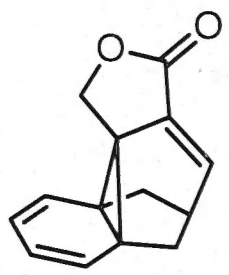


1.13

Figure 1.3. Salvinorin A (**1.12**), salvileucalin B (**1.3**) and the potential pharmacophore, *viz*. the caged core lactone **1.13**, associated with the latter.

1.4. Previous Synthetic Studies of Salvileucalin B

Since its isolation in 2008, two research groups have published work directed towards the total synthesis of salvileucalin B (**1.3**). In early 2010, the Reisman group published the outcome of studies on the assembly, in racemic form,[15] of the caged core **1.14** and, one year later, the enantioselective total synthesis[16] of salvileucalin B itself, with the route to the latter proceeding *via* lactone **1.15** (Figure 1.4). Shortly thereafter Chen *et al.* published their enantioselective synthesis[7] of the propellane **1.16** together with the elaboration of this into more complex derivatives including lactone **1.17**.

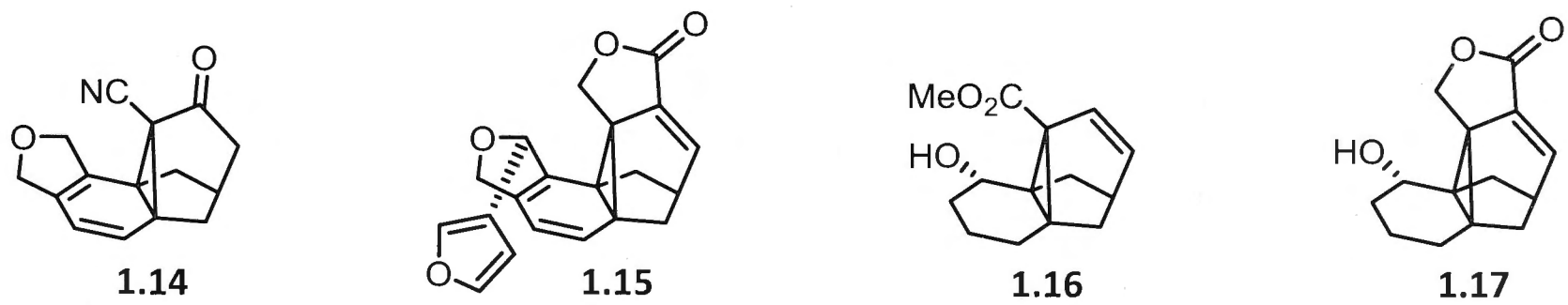


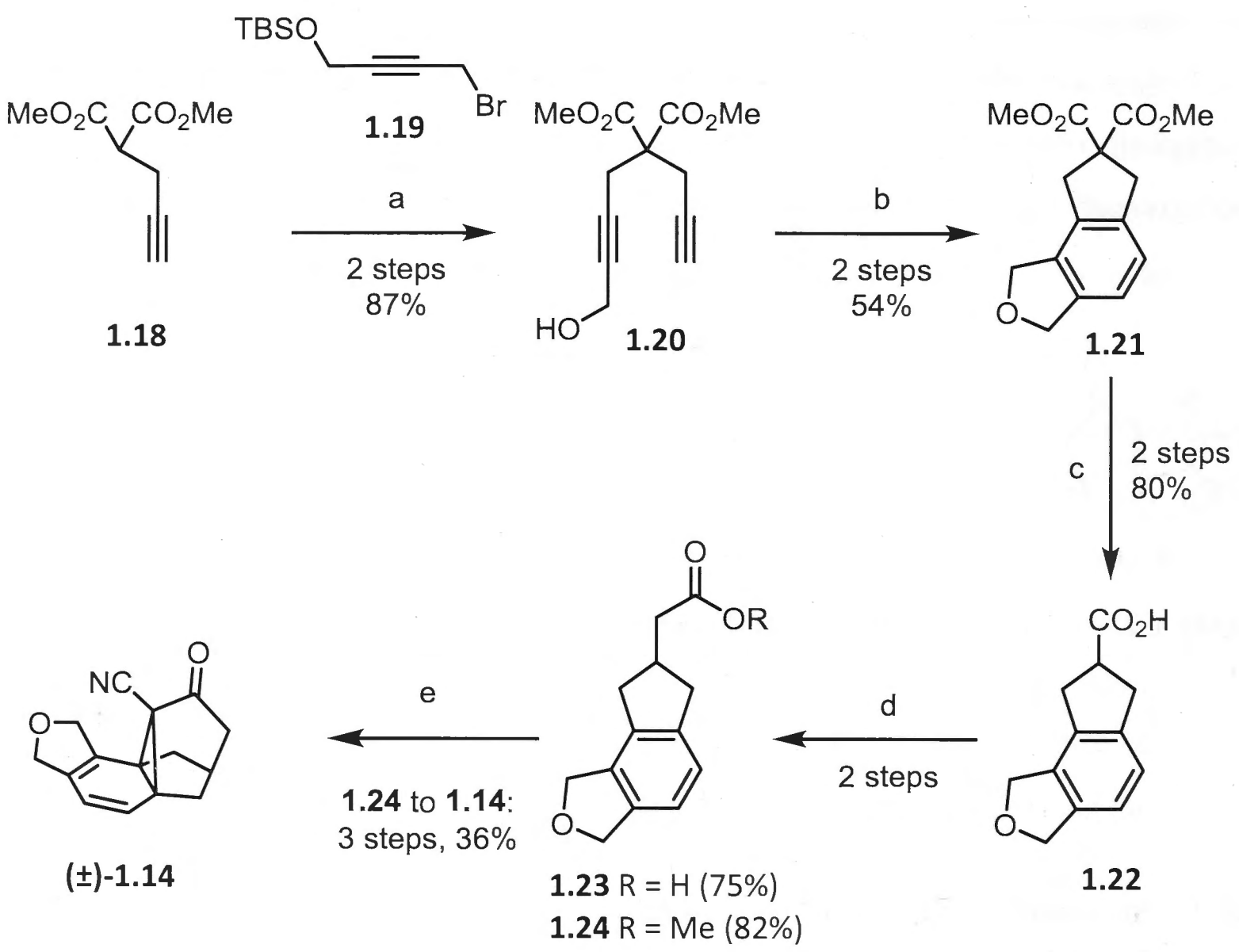
Figure 1.4. Caged cores and lactones reported by the Reisman and Chen groups.

1.4.1. Reisman's Synthesis of the Caged Core and (+)-Salvileucalin B (1.3)

The Reisman group's approach to the racemic form of the caged core substructure of (+)-salvileucalin B (**1.3**) is shown in Scheme 1.2. Thus, commercially available malonate **1.18** was alkylated with bromide **1.19** and the product of this process then deprotected to afford diyne **1.20**. Ether formation followed using propargyl bromide to give a triyne that cyclised in the presence of $Pd(PPh_3)_4$ to form tricycle **1.21**. Decarboxylation and saponification of the last compound gave acid **1.22** that was, in turn, subjected to an Arndt-Eistert homologation protocol to form either acid **1.23** (R = H) or corresponding ester **1.24** (R = Me), depending on whether water or methanol was added to the reaction mixture.

The key step for the formation of the core structure within target **1.3** was an intramolecular arene cyclopropanation - or Büchner reaction - of the intermediate diazocarbonyl compound that provided compound **1.14** in racemic form. The yield for this reaction was strongly dependent on the functional groups present at the newly formed ring-junction. Thus, when ester **1.24** was elaborated so as to incorporate a nitrile residue, the yield of the Büchner reaction was 64%. When acid **1.23** was elaborated into analogues of compound **1.14** containing a methyl group or a methyl ester in place of the nitrile then the yield of the Büchner process dropped to less than 10%. This variation is attributed to the adverse steric effects of

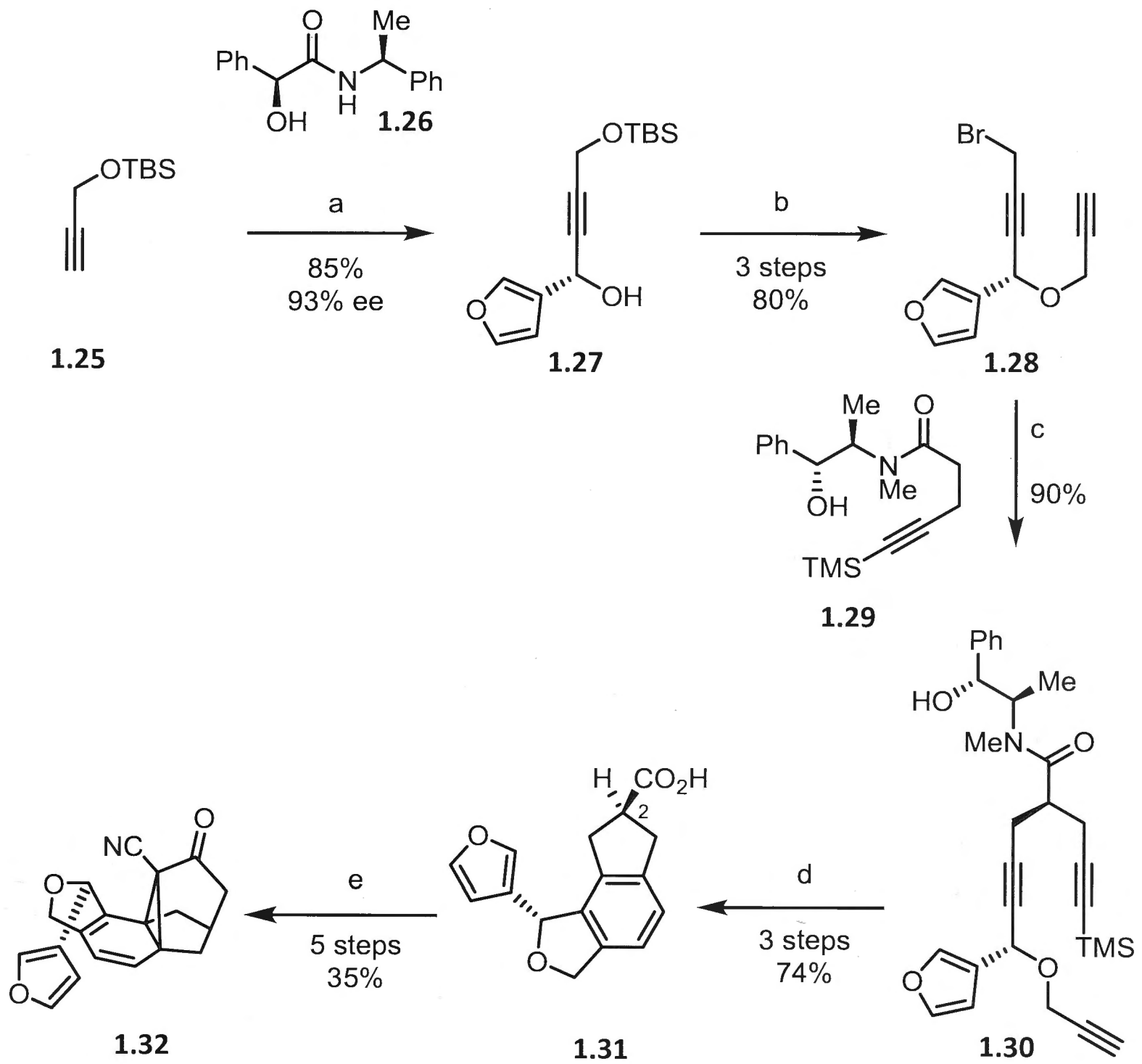
the methyl and methyl ester moieties. Overall, the nitrile-containing caged core **1.14** was synthesised from malonate **1.18** in 9 steps and in 17% combined yield.



Scheme 1.2. *Reagents and Conditions*: (a) i. NaH, **1.19**, THF; ii. 1 M aq. HCl, MeOH; (b) i. NaH, propargyl bromide; ii. $Pd(PPh_3)_4$, AcOH, MeCN, 80 °C; (c) i. NaCl, H_2O, DMSO, 150 °C; ii. KOH, MeOH, H_2O; (d) i. $(COCl)_2$, cat. DMF, CH_2N_2, DCM; ii. AgTFA, ROH, Et_3N, THF, −25 °C; (e) i. $LiCH_2CN$, THF, −78 °C; ii. imidazolesulfonyl azide, pyridine, MeCN; iii. $Cu(hfacac)_2$, DCM, μwave, 120 °C.

The enantioselective total synthesis (Scheme 1.3) of the natural product itself, *viz*. compound **1.3**, exploits the just mentioned chemistry and starts with the commercially available TBS-protected propargyl alcohol **1.25**. This was alkylated in an enantioselective 1,2-addition of the derived zinc acetylide to 3-furaldehyde in the presence of the chiral ligand **1.26** and so affording compound **1.27** in 93% ee. *O*-Propargylation followed by TBS-deprotection, mesylation and nucleophilic substitution of the mesylate group so as to install a propargylic bromide gave diyne **1.28**. Subjection of this last compound to reaction with the enolate derived from compound **1.29** yielded the enantioenriched triyne **1.30** that cyclised in the same manner as before but now giving the tricyclic compound **1.31**. Functional group interconversions were followed by the Büchner reaction. This proceeded stereoselectively due

to the influence of the C2 substituents and thus affording the caged core compound **1.32** in 13 steps and 16% overall yield.

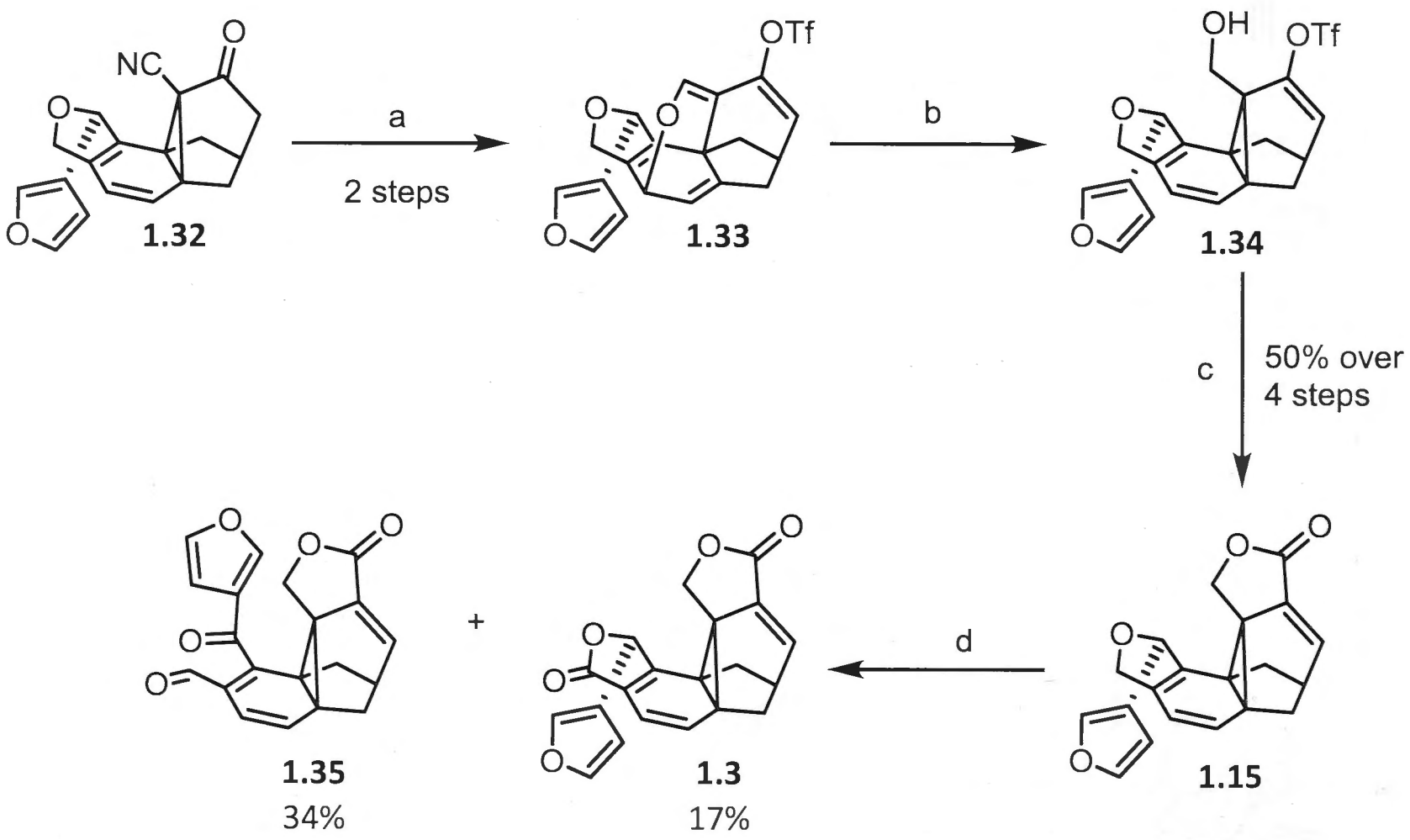


Scheme 1.3. *Reagents and Conditions*: (a) Me_2Zn, **1.26**, toluene, 70 °C, 3-furaldehyde, 0 °C to rt; (b) i. NaH, propargyl bromide, DMF; ii. 1 M HCl, MeOH; iii. MsCl, NEt_3, THF, then LiBr; (c) LiHMDS, **1.29**, LiCl, THF, −78 °C to rt; (d) i. TBAF, DCM; ii. RuCp*(cod)Cl, DCM, 40 °C; iii. *n*-Bu_4NOH, *t*-BuOH/H_2O, 90 °C; (e) i. $(COCl)_2$, cat. DMF, CH_2N_2, THF; ii. AgTFA, MeOH, Et_3N, THF, −30 °C to rt; iii. $NaCH_2CN$, THF, −78 °C to rt; iv. imidazole sulfonyl azide, pyridine, MeCN; v. $Cu(hfacac)_2$, DCM, μwave, 120 °C.

Construction of the lactone substructures was achieved by converting the ketone moiety within compound **1.32** into the corresponding enol triflate (Scheme 1.4) and subjecting this to a two-fold DIBAL-H reduction protocol so as to transform the nitrile group into the corresponding alcohol. The first of these reductions was followed by what was thought to be a reversible retro-Claisen rearrangement (*vide infra*) to give compound **1.33**.[‡] The second DIBAL-

[‡] Work undertaken by the author, as described in Chapter 3, suggests this structure is incorrect.

H mediated reduction step furnished the target primary alcohol **1.34** (57% yield over two steps) which engaged in a palladium-catalysed carbonylative coupling reaction to give lactone **1.15**. In the final step of the reaction sequence the dihydrofuran ring of compound **1.15** was oxidised to form, along with the over-oxidised by-product **1.35**, the target lactone and thus completing the first enantioselective total synthesis of (+)-salvileucalin B (**1.3**). This took place in 18 steps and was achieved in an overall yield of 4%.

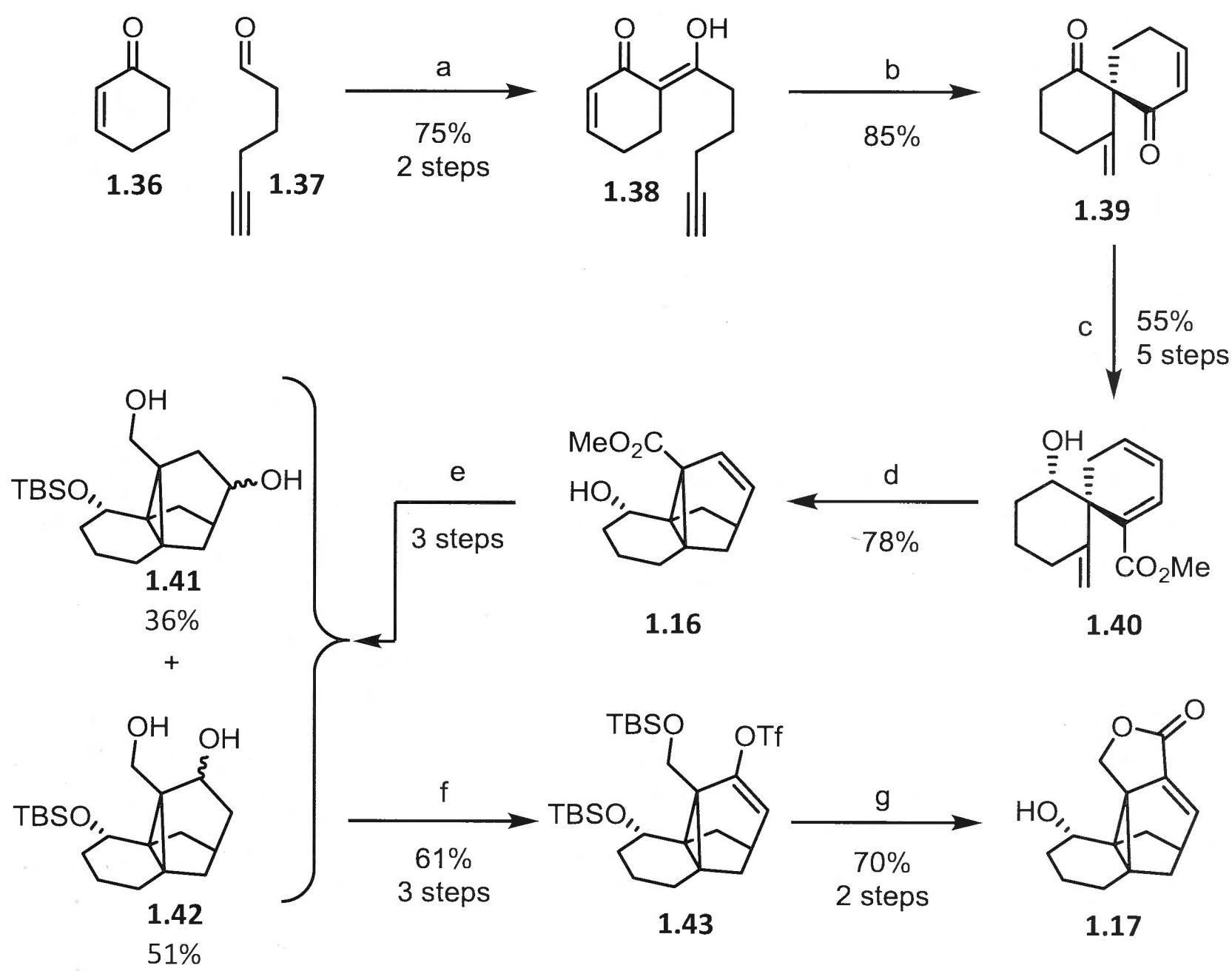


Scheme 1.4. *Reagents and Conditions*: (a) i. NaHMDS, $PhNTf_2$, −78 °C; ii. DIBAL, DCM, −40 °C, then 5% aq. AcOH; (b) DIBAL, DCM, −40 °C, then 5% aq. AcOH; (c) $Pd_2(dba)_3$, dppf, CO (1 atm), DIPEA, THF; (d) chromium trioxide-3,5-dimethylpyrazole complex, DCM, −35 °C.

1.4.2. Chen's Approach Towards the Total Synthesis of Salvileucalin B (1.3)

Chen's approach mimicked the key step of the proposed biosynthetic pathway leading to salvileucalin B and in which it is suggested that spiro compound **1.11** (see Scheme 1.1 on page 3) undergoes an intramolecular Diels-Alder (IMDA) cycloaddition reaction to form the caged core structure of the natural product. Thus, the synthetically-derived spirocycle **1.39** (Scheme 1.5) was generated through a Conia-ene reaction of compound **1.38** that was itself prepared through aldol condensation of cyclohex-2-en-1-one (**1.36**) with aldehyde **1.37** followed by Dess-Martin oxidation. Installation of protecting groups, functional group interconversions and deprotection then furnished the spirocycle **1.40** in 55% yield over five

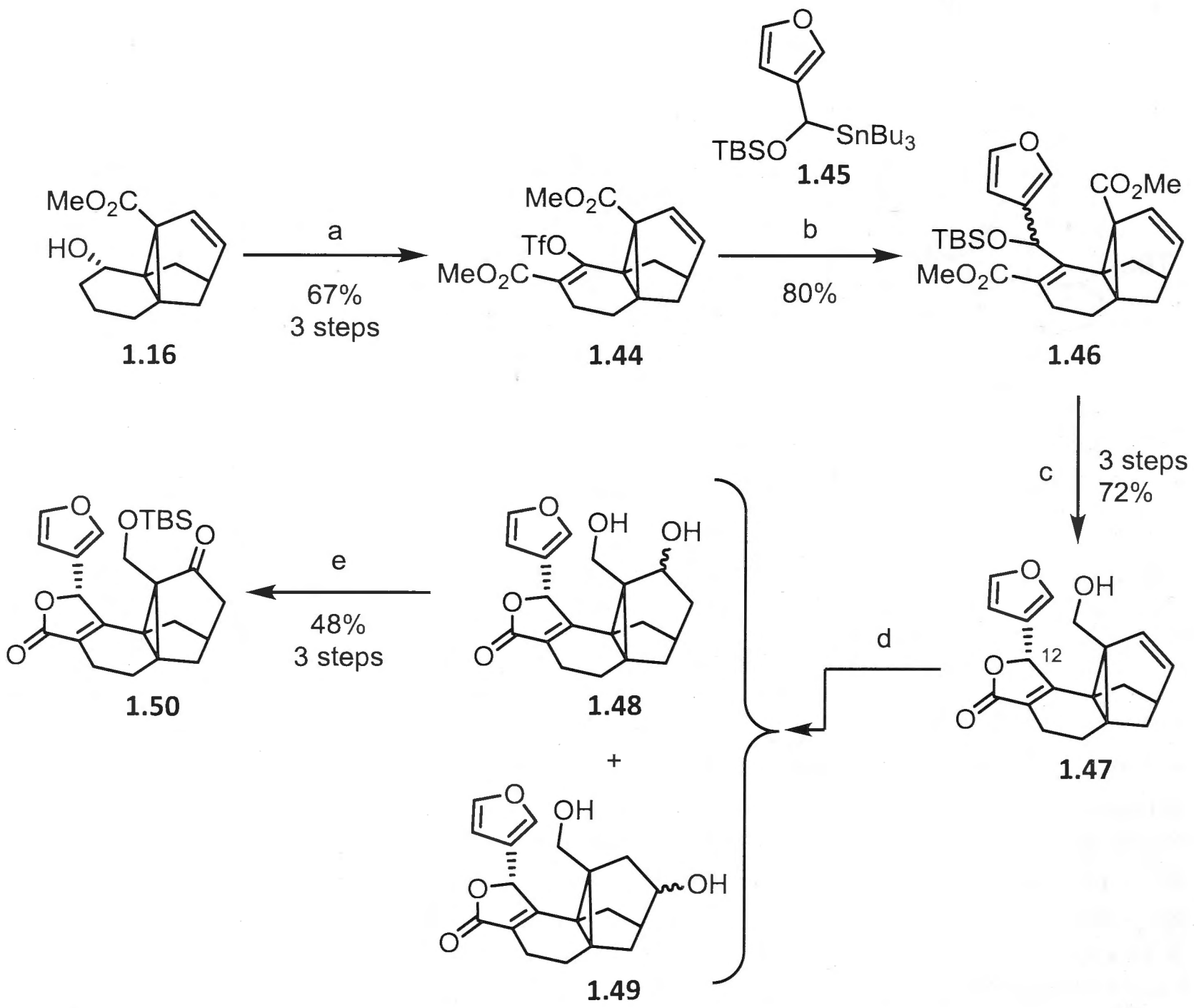
steps. The anticipated IMDA reaction proceeded upon microwave heating of triene **1.40** at 250 °C to give the desired caged core intermediate **1.16** in 78% yield. TBS-protection of the hydroxyl group and DIBAL-H reduction of the methyl ester residue within compound **1.16** was followed by hydroboration/oxidation of the C-C double bond to give the two isomeric diols **1.41** and **1.42** in 40% and 55% yield, respectively. TBS-protection and various functional group interconversions of diol **1.42** then gave enol triflate **1.43**. The required α-methylenebutyrolactone ring was then installed through palladium-catalysed carbonylative coupling and, after global deprotection, the hydroxylated caged core lactone **1.17** was obtained in 6% yield over 17 steps.



Scheme 1.5. *Reagents and Conditions*: (a) i. LDA, THF; ii. DMP, DCM; (b) ZnI_2, toluene; (c) i. DIBAL-H, THF; ii. TBSOTf, DCM; iii. KHMDS, $PhNTf_2$, THF; iv. $Pd(PPh_3)_4$, CO, MeOH; v. HF•py, THF; (d) μwave, 1,2-dichlorobenzene, 250 °C; (e) i. TBSOTf, DCM; ii. DIBAL-H, DCM; iii. BH_3•THF; (f) i. TBSCl, DMF; ii. DMP, DCM; iii. KHMDS, $PhNTf_2$, THF; (g) i. $Pd(PPh_3)_4$, CO, MeOH; ii. HF•py, THF.

Various attempts to convert the alcohol moiety within compound **1.17** into the desired furan-substituted lactone failed. Thus, the extant lactone moiety was unstable to all tested reaction

conditions used in efforts to effect the key coupling step that, it had been hoped, would allow for installation of the required furan moiety. As a result, the installation of the second lactone and the associated furan ring was carried out by starting with the caged core ester **1.16** (Scheme 1.6). Oxidation of the alcohol function followed by subjection of the ensuing ketone to reaction with Mander's reagent with subsequent formation of the enol triflate gave the carbomethoxy-substituted enol triflate **1.44**. This was subjected to reaction with stannane **1.45** in the presence of NMP to give the product **1.46** in 80% yield. TBS-deprotection of compound **1.46** resulted in spontaneous lactonisation and so completing the installation of the second heterocyclic ring. DIBAL-H mediated reduction and subsequent selective TEMPO oxidation, to reinstall the lactone moiety, yielded alcohol **1.47** and its C12-epimer, that could be separated from one another using chromatographic methods. Subjection of compound **1.47** thus obtained to hydroboration/oxidation yielded a 3.5:1 mixture of the two isomeric diols **1.48** and **1.49**. TBS-protection of the primary alcohol residue within diol **1.48** was followed by Dess-Martin oxidation of the remaining (unprotected) secondary alcohol to give compound **1.50**.



Scheme 1.6. *Reagents and Conditions*: (a) i. DMP, DCM; ii. LiHMDS, Mander's reagent; iii. NaH, Comin's reagent, DME; (b) **1.45**, NMP; (c) i. HF•py, MeCN; ii. DIBAL-H, DCM; iii. TEMPO, PIDA, DCM; (d) BH_3•THF; (e) i. TBSCl, DMF; ii. DMP, DCM.

Compound **1.50** was thereby obtained in 19 steps and 5% overall yield. The installation of the remaining lactone residue can most likely be accomplished using the same end-game chemistry as employed by Reisman *et al.*[16] This would require three pivotal steps, namely TBS-deprotection, conversion of the ketone into the enol triflate and palladium-catalysed carbonylative coupling. However, Chen *et al.* did not provide any suggestions about precisely how the second C-C double bond of the cyclohexadiene moiety could be installed so as to complete such a total synthesis.

The concomitant studies that were carried out by the author in an effort to establish a total synthesis of the natural product salvileucalin B (**1.3**) and, *en route*, of the putative pharmacophore compound **1.13** are presented in Chapter 2.

1.5. References

(1) Esquivel, B.; Dominguez, R. M.; Hernández-Ortega, S.; Toscano, R. A.; Rodríguez-Hahn, L. *Tetrahedron* **1994**, *50*, 11593.

(2) Narukawa, Y.; Hatano, K.; T., T. *J. Nat. Med.* **2006**, *60*, 206.

(3) Aoyagi, Y.; Yamazaki, A.; Nakatsugawa, C.; Fukaya, H.; Takeya, K.; Kawauchi, S.; Izumi, H. *Org. Lett.* **2008**, *10*, 4429.

(4) Aoyagi, Y.; Yamazaki, A.; Kato, R.; Tobe, F.; Fukaya, H.; Nishikawa, T.; Nakahashi, A.; Miura, N.; Monde, K.; Takeya, K. *Tetrahedron Lett.* **2011**, *52*, 1851.

(5) Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243.

(6) a) Kelly, W. L. *Nature* **2011**, *473*, 35; b) Kim, H. J.; Ruszczycky, M. W.; Choi, S.-h.; Liu, Y.-n.; Liu, H.-w. *Nature* **2011**, *473*, 109.

(7) Tseng, C.-C.; Ding, H.; Li, A.; Guan, Y.; Chen, D. Y. K. *Org. Lett.* **2011**, *13*, 4410.

(8) Tantillo, D. J. *Org. Lett.* **2010**, *12*, 1164.

(9) Liu, H.-J.; Shia, K.-S.; Han, Y.; Sun, D.; Wang, Y. *Can. J. Chem.* **1997**, *75*, 646.

(10) Ortega, A.; Blount, J. F.; Manchand, P. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, *10*, 2505.

(11) a) Lovell, K. M.; Prevatt-Smith, K. M.; Lozama, A.; Prisinzano, T. E. *Chemistry of Opioids*; Springer Verlag, 2011; Vol. 299; b) Lingham, A. R.; Hügel, H. M.; Rook, T. J. *Aust. J. Chem.* **2006**, *59*, 340; c) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968; d) Burns, A. C.; Forsyth, C. J. *Org. Lett.* **2008**, *10*, 97; e) Nozawa, M.; Suka, Y.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2008**, *10*, 1365.

(12) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426.

(13) Heinrich, N.; Banwell, M. G.; Willis, A. C.; Cade, I. A.; Capon, R. J.; Huang, X.-C. *Aust. J. Chem.* **2012**, *65*, 1679.

(14) Van Drie, J. H. *Internet Electron J. Mol. Des.* **2007**, *6*, 271.

(15) Levin, S.; Nani, R. R.; Reisman, S. E. *Org. Lett.* **2010**, *12*, 780.

(16) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774.

Chapter 2

Synthesis of the Caged Core Lactone of Salvileucalin B

2.1. Retrosynthetic Analyses

Arguably, the [4.3.1]propelladiene core within salvileucalin B (**1.3**) (see substructure highlighted in blue in Figure 2.1) presents the greatest synthetic challenge associated with this target natural product. It seemed appropriate, therefore, to first concentrate on assembling this caged framework and the attached "northern lactone" as embodied within compound **1.13** and to subsequently functionalise the diene moiety so as to introduce the second lactone unit and the single furan ring. The three most straightforward retrosynthetic disconnections considered for the assembly of this core are shown in Figure 2.1. The first possibility was to cleave (in a retrosynthetic sense) the α-methylene residue of the α-methylene-γ-butyrolactone moiety (Path A) and so resulting in the identification of aldehyde **2.1** as a potential precursor. This meant that the cyclopropane moiety had to be installed at an early stage in the synthesis, something that could be achieved, at least in principle, through addition of a dihalocarbene to the C-C double bond of a dihydroindane derivative such as diene **2.3** and thus producing the [4.3.1]propellane **2.2**. Another option was to cleave the cyclopropane ring (Path B) and so resulting in a diazo-containing substrate of the general form **2.4** as a precursor. Since the diazo-transfer reactions normally used to construct such precursors can only be performed at the α-position of an enolisable carbonyl moiety an anhydride was the necessary precursor if installation of the northern lactone was to be accomplished at an early stage. This would present the challenge of having to selectively remove a carbonyl moiety following the cyclopropanation event. Path C shows a third means by which the formation of the caged core lactone could be achieved. This involves, in effect, combining the approaches shown in Paths A and B, and so installing the cyclopropane moiety using diazo-substituted anhydride **2.5** as the substrate and engaging this in an intermolecular cyclopropanation reaction with diene **2.6**. This would be followed by aldol condensation of the aldehyde moiety with the enolisable anhydride carbonyl. However, this pathway suffers from the disadvantages of requiring

selective removal of the anhydride carbonyl after the cyclopropanation event as well as the need for the carbenoid to add to the more substituted of the two C-C double bonds within diene **2.6**.

Due to the extensive utilisation of *gem*-dibromocyclopropanes as building blocks in natural product synthesis within the Banwell group[1] Path A was chosen for initial study. Details of the outcomes thus obtained are presented in Section 2.2 on the following pages.

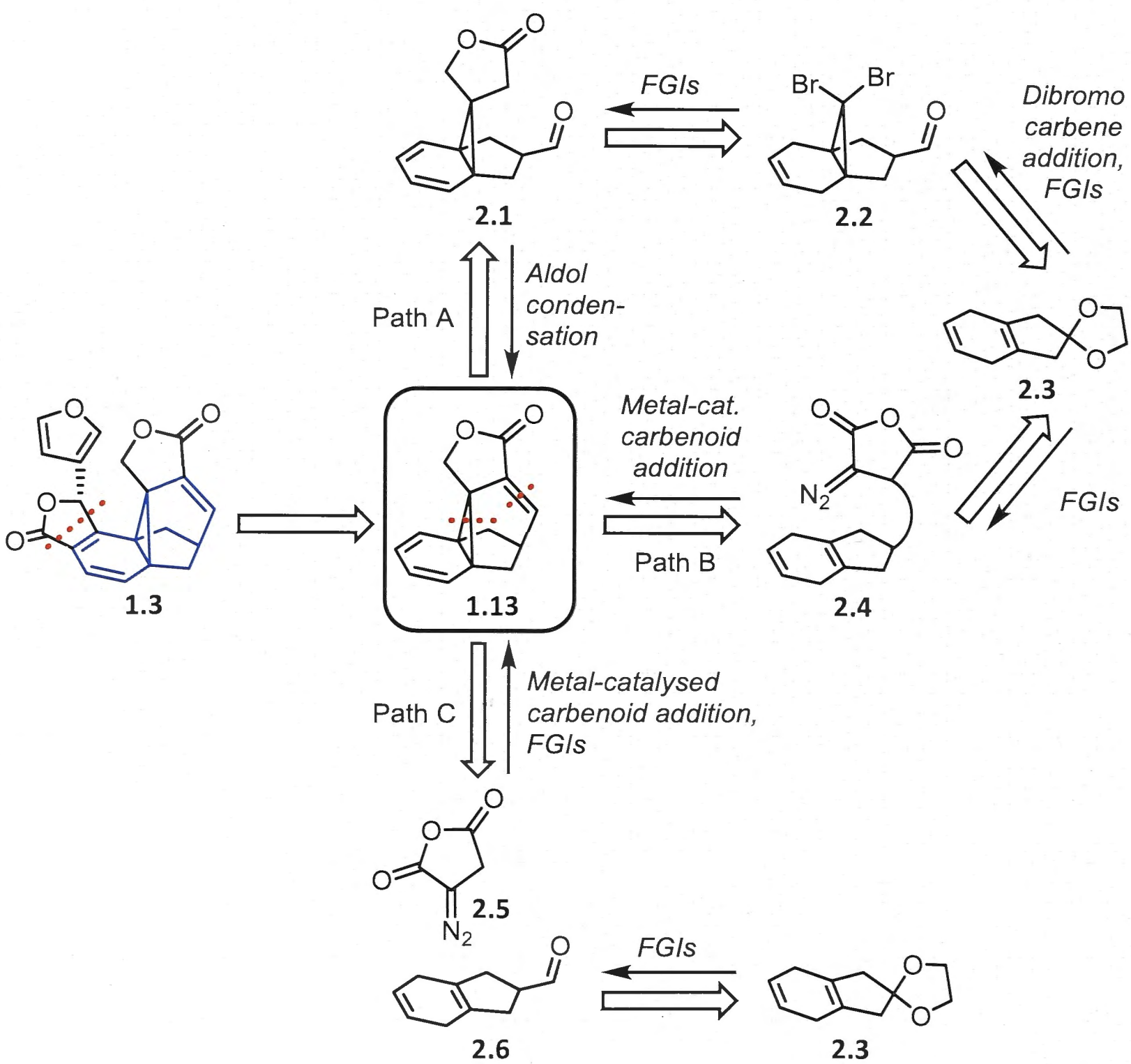
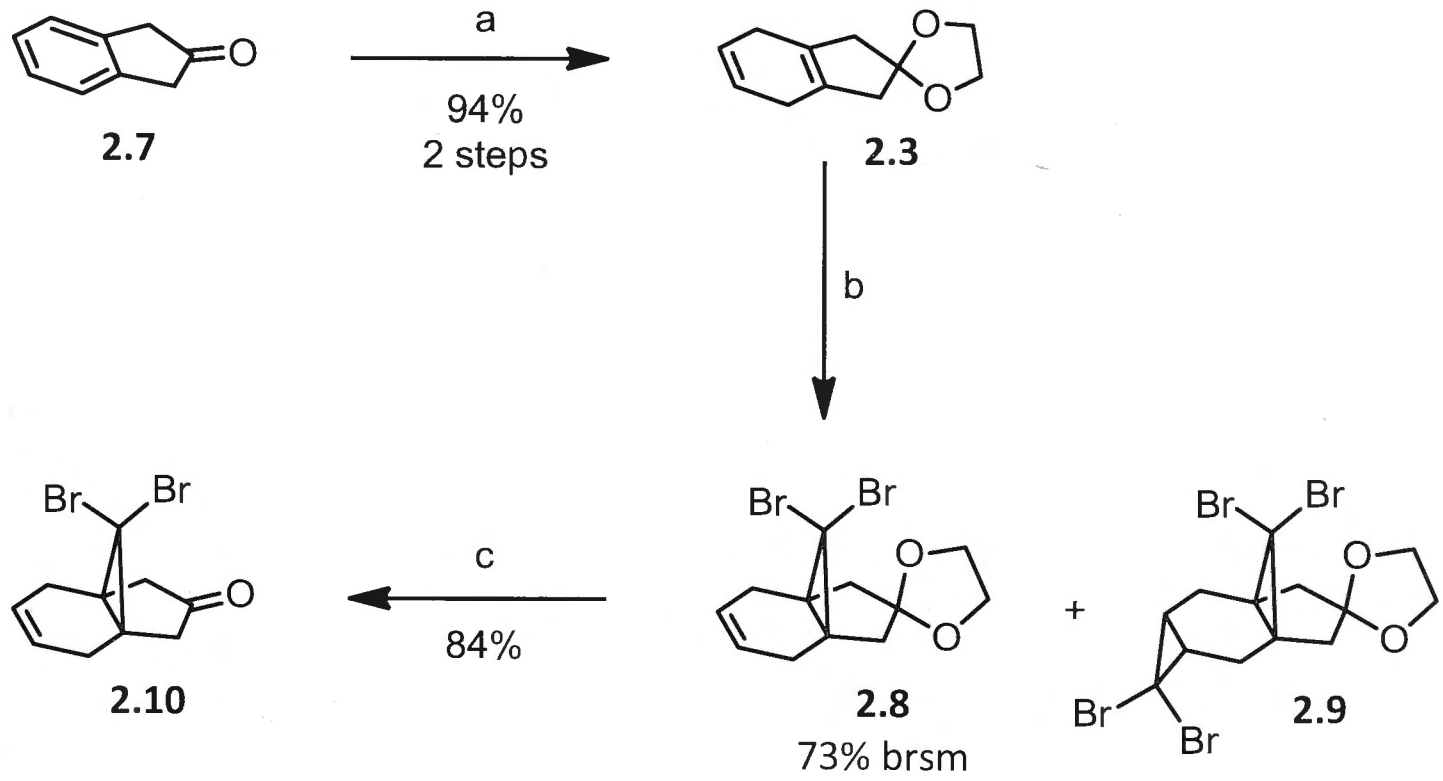


Figure 2.1. Three possible retrosynthetic disconnections of the C_2-symmetric caged core lactone **1.13**.

2.2. First Generation Approach: Dibromocyclopropane Formation and Reactivity

The reaction sequence used to generate the [4.3.1]propellane required for investigating the approach to target **1.3** defined by Path A in Figure 2.1 is shown in Scheme 2.1. Thus, commercially available 2-indanone (**2.7**) was quantitatively converted into the known ethylene ketal and this was, in turn, subjected to Birch reduction conditions to form diene **2.3** in 94% yield.[2] The synthesis of [4.3.1]propellane **2.8**, the dichloro-analogue of which has been reported previously,[3] required the addition of dibromocarbene to the more substituted and, thus, more electron-rich C-C double bond within diene **2.3**. The required carbene could be generated from bromoform in the presence of base. A variety of bases were tested for this purpose (including aqueous NaOH, NaOH pellets in DCM, and *t*-BuOK) at different temperatures and in various solvents. It was found that the portionwise addition of *t*-BuOK to a solution of diene **2.3** and bromoform in hexane gave the best yield (55% at 75% conversion) of the target propellane **2.8**. The selectivity of the carbene addition reaction was poor at room temperature and usually 10-20% of bis-adduct **2.9** was isolated, an outcome that could be avoided by carrying out the reaction at 0 °C.

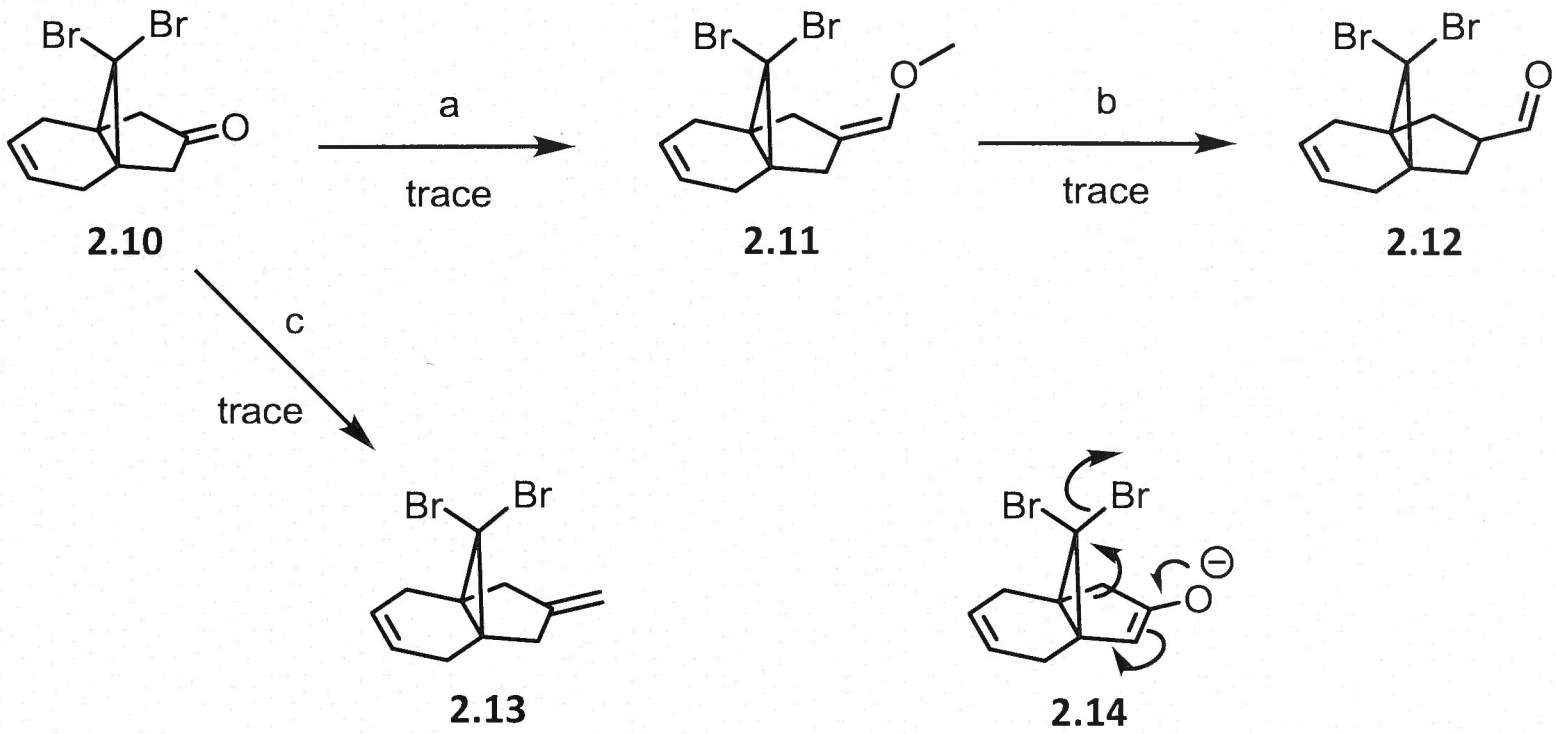


Scheme 2.1. *Reagents and Conditions*: (a) i. ethylene glycol, *p*-TsOH•H_2O, benzene, reflux; ii. Li, NH_3, EtOH, THF, −78 °C to −33 °C; (b) $CHBr_3$, *t*-BuOK, *n*-hexane, 0 °C to rt; (c) dilute aq. HCl, THF, reflux.

The ketal moiety within adduct **2.8** was then cleaved by treating it with dilute acid to give the light- and air-sensitive ketone **2.10** in 84% yield. All of the spectroscopic data obtained on this material were in accord with the assigned structure. Specifically, its symmetrical nature was

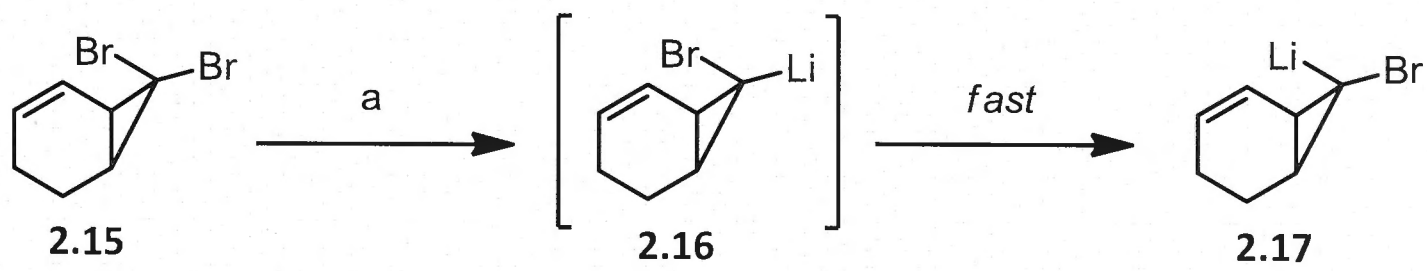
readily established. Thus, for example, in the ^{13}C NMR spectrum of this material a single olefinic carbon resonance was observed at δ 123.1 while the signal due to the dibromo-substituted carbon of the cyclopropane moiety was visible at δ 53.6. The ketone carbonyl carbon appeared at δ 213.5 and the presence of this moiety was also confirmed by IR spectroscopy.

Attempts to subject ketone **2.10** to a Wittig olefination[4] reaction with the ylide derived from (methylmethoxy)triphenylphosphonium chloride (Scheme 2.2) only yielded a complex mixture of products within which triphenylphosphine oxide was the only identifiable component. Despite numerous efforts to isolate any of the many other products of reaction no evidence for the formation of the desired methyl vinyl ether **2.11** was obtained. When the crude mixture was subjected to (acidic) silica gel during attempted flash column chromatographic purification, traces of a compound were obtained that showed a signal in the "aldehyde region" of the ^{1}H NMR spectrum. On that basis, the crude product mixture from the Wittig olefination reaction, presumed to contain compound **2.11**, was subjected to reaction with dilute acid, in an effort to cleave the associated methyl vinyl ether moiety. However, none of the desired aldehyde **2.12** was obtained. Other olefination protocols such as a $Zn/TiCl_4$-mediated[5] or Wittig-type methylenation of ketone **2.10** were attempted but only complex mixtures containing, at best, traces of the desired compound **2.13** were obtained. This failure to form the desired product is most likely due to the competing fragmentation of the cyclopropane ring within compound **2.10**. Specifically, in the presence of base the enolate **2.14** is formed, and this can then fragment in the illustrated manner with accompanying ejection of a bromide ion. The highly strained bridgehead olefins resulting from such a fragmentation process presumably then engage in a range of dimerisation and nucleophilic addition reactions.[6]



Scheme 2.2. *Reagents and Conditions*: (a) (methylmethoxy)triphenylphosphonium chloride, *s*-BuLi, THF, 0 °C; (b) silica gel, rt; (c) i. CH_2I_2, $TiCl_4$, Zn; or ii. CH_3PPh_3Br, various bases.

In an alternate approach that acknowledges the base-sensitivity of ketone **2.10**, a stepwise halogen-lithium exchange[7] of the *gem*-dibromocyclopropyl moiety within the base-stable ketal **2.8** was pursued. In this context it is appropriate to note that Warner *et al.*[6a] found that when performing a bromine/lithium exchange on *gem*-dibromo compound **2.15** (Scheme 2.3) the less sterically hindered bromide was exchanged first to give intermediate **2.16** but this was followed by an isomerisation process that placed the lithium over the six-membered ring (*i.e.* in an *endo*-orientation). They concluded that this latter carbenoid **2.17** was the thermodynamically more stable one because the smaller lithium occupies the sterically more demanding *endo*-position at the apex of the cyclopropane ring.

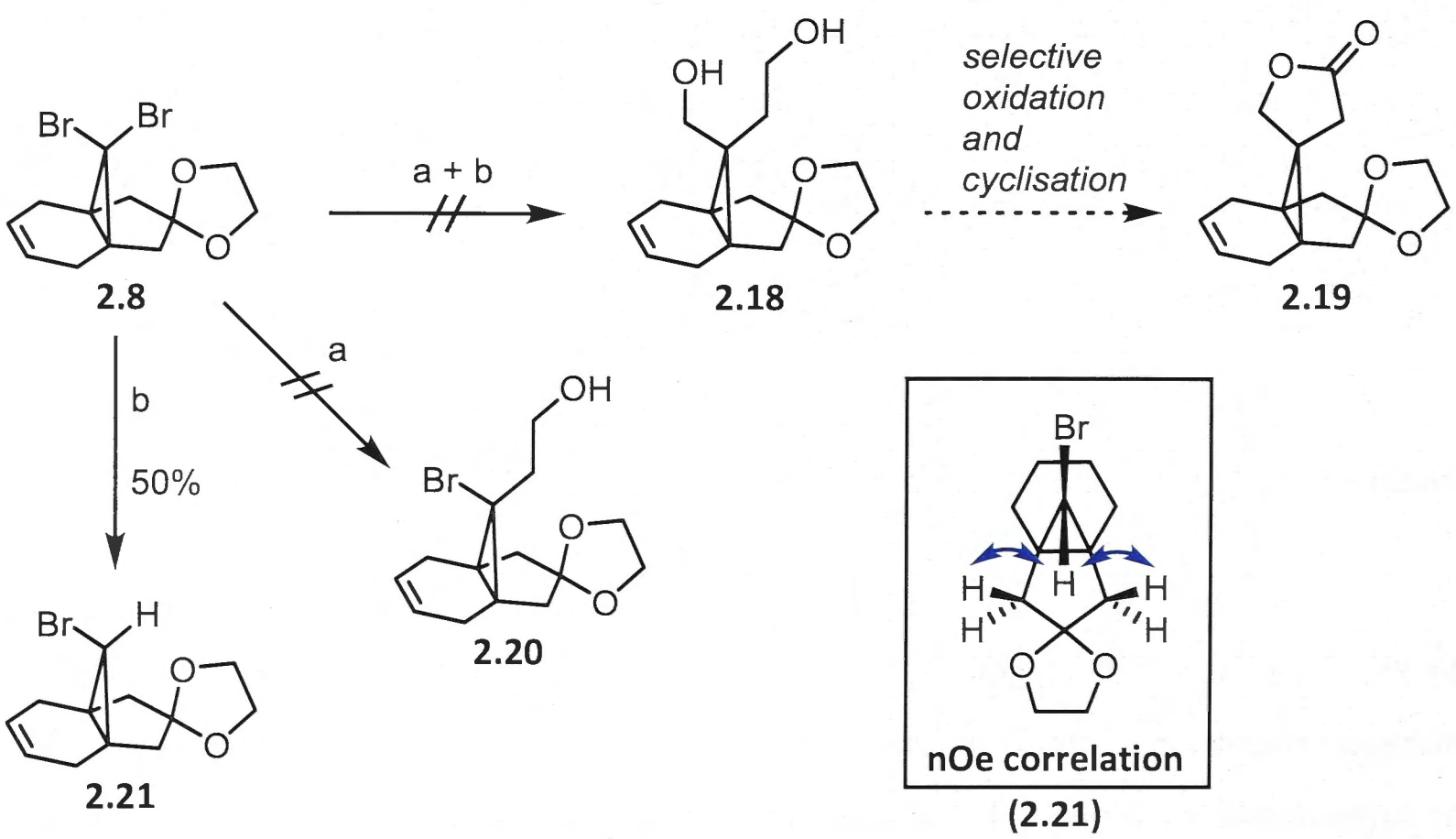


Scheme 2.3. *Reagents and Conditions*: (a) *n*-BuLi, THF, −100 °C.

On this basis, it was envisaged that the geminally-related halogens of compound **2.8** would undergo selective Br/Li-exchange because the acetal oxygen could provide a coordination site for lithium and so prevent the above-mentioned epimerisation process. Thus, the mono-lithiated species that has the metal atom directed towards the proximate acetal oxygen should

be more thermodynamically stable than its epimer. Addition of ethylene oxide to this nucleophilic carbenoid would then occur at the site of lithiation and so install a two-carbon residue that could be used to construct the target lactone. A second Br/Li-exchange followed by addition of paraformaldehyde could then be used to install a further one-carbon fragment and deliver diol **2.18**. Through selective oxidation and functionalisation of the alcohol moieties within compound **2.18** and, in particular, by exploiting the likely greater reactivity of the less congested primary alcohol moiety, it was hoped lactone **2.19** could be obtained.

In order to investigate this approach, a solution of dibromocyclopropane **2.8** in freshly distilled THF was cooled to −95 °C then treated successively with an organo-lithium reagent (as specified below) and ethylene oxide (Scheme 2.4). The reaction mixture was then warmed to −78 °C and *n*-BuLi was added followed by paraformaldehyde. However, this sequence of reactions failed to deliver either intermediate **2.20** or the desired diol **2.18**. Instead, a complex mixture of materials was obtained. Employing *n*-, *s*-, or *t*-BuLi as the initial reagent as well as varying the reaction temperature failed to change the outcome of such reactions. When a single Br/Li-exchange process was carried out and followed by addition of just formaldehyde then the mono-dehalogenated compound **2.21** was obtained in 50% yield. The stereochemistry at the apex of the cyclopropane ring within this last compound was established using nOe experiments and wherein a correlation was observed between the proton at the apical position and the β-oriented hydrogen of each of the cyclopentane methylene groups (as indicated by the blue arrows).



Scheme 2.4. *Reagents and Conditions*: (a) *n*-BuLi, ethylene oxide, −95 °C, THF; (b) *n*-BuLi, paraformaldehyde, −78 °C, THF.

This result supports the notion that coordination by the acetal oxygen directs initial lithiation at the desired position. However, the ensuing lithiated species clearly did not react with either of the two electrophiles (*viz*. ethylene oxide and paraformaldehyde) added to the reaction mixtures before the quenching step.

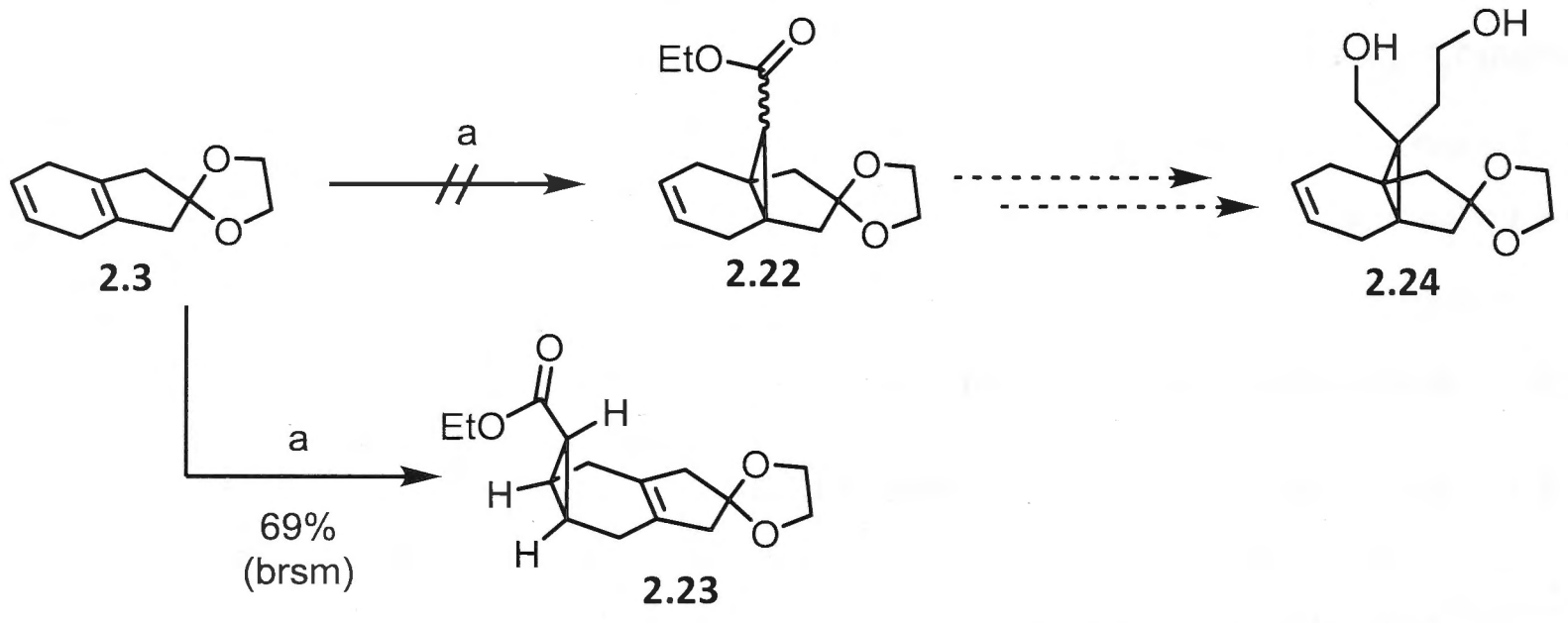
Since neither of the hoped-for manipulations of the *gem*-dibromocyclopropane or ketone moieties within compounds **2.8** and **2.10**, respectively, was successful, a different approach to target **1.13** was clearly required. As such, Pathways B and C shown in Figure 2.1 were now pursued.

2.3. Second Generation Approach: Exploiting Diazocarbonyl Chemistry

2.3.1. The Intermolecular Carbenoid Addition Approach

In the approach delineated immediately below it was hoped that the carbenoid derived from the metal-mediated extrusion of nitrogen from a diazocarbonyl-containing compound[8] such as diazosuccinic anhydride **2.5** (see Figure 2.1) or ethyl diazoacetate, would chemoselectively add to the more substituted and, thus, more electron-rich double bond of the cyclohexa-1,4-diene moiety within compound **2.3**. That having been said, the sterically congested environment about the central C-C double bond was expected to play a part in determining the regioselectivity of the cyclopropanation process. In particular, the less substituted C-C double bond is likely to be more accessible because it is on that side of the molecule remote from the substituted cyclopentene and, therefore, the steric effects exerted by the ketal moiety of compound **2.3**. In order to test if carbenoid addition to the desired C-C double bond was possible at all, ethyl diazoacetate was used rather than the more bulky anhydride **2.5** which already embodies the precursor to the lactone. If the formation of the hoped-for compound **2.22** was successful, functional group interconversions could then lead to diol **2.24**. Encouragingly, Hopf and co-workers[9] used ethyl diazoacetate in forming a related [4.3.1]propellane. Based on these observations it was hoped reaction conditions could be defined so as to favour attack on the more substituted double bond of cyclohexa-1,4-diene **2.3** and so generating propellane **2.22**, rather than isomer **2.23** (Scheme 2.5). In the event, however, when cyclohexa-1,4-diene **2.3** was subjected to reaction with ethyl diazoacetate in the presence of anhydrous $CuSO_4$, $Cu(acac)_2$ or $Rh_2(OAc)_4$, it was found that the ensuing carbenoid only added to the less-substituted double bond to give compound **2.23**. This was obtained as a single diastereomer in 69% yield (brsm). The resonance due to the apical cyclopropyl proton appeared as a triplet and the magnitude of the coupling constant (4.4 Hz)

suggested a *trans*-relationship with the remaining protons on the three-membered ring. No evidence for the formation of the desired [4.3.1]propellane **2.22** was obtained. In an effort to change the outcome of the reaction it was run at 0 °C but under such conditions the ethyl diazoacetate simply dimerised and so the starting diene was recovered in almost quantitative yield.



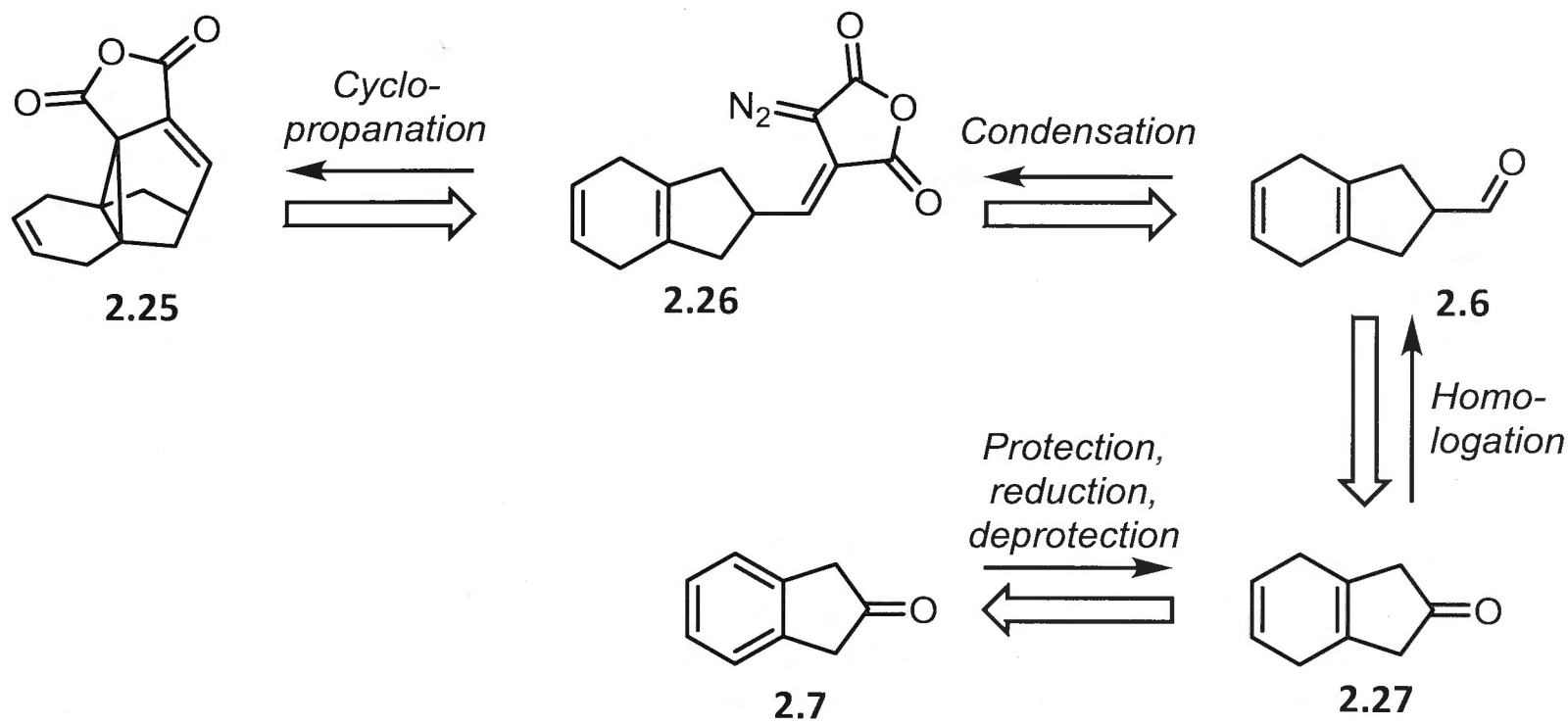
Scheme 2.5. *Reagents and Conditions*: (a) ethyl diazoacetate, $Rh_2(OAc)_4$ (2 mol%), DCM, rt, slow addition.

Efforts to epoxidise the "outer" C-C double bond within compound **2.3** in order to then effect diazocarbenoid addition at the remaining, internal, double bond were also unsuccessful. Conversely, and perversely, in this instance, epoxidation only occurred at the internal double bond. Accordingly, an intramolecular cyclopropanation approach that would ensure addition of the relevant carbenoid to the more substituted (internal) double bond was investigated.

2.3.2. The Intramolecular Carbenoid Addition Approach

A seemingly viable solution to the abovementioned problems of regiocontrol was to carry out the carbenoid addition reaction in an intramolecular fashion.[8] The tether connecting the diazocarbonyl-containing residue to the diene moiety would restrict the carbenoid's reach and was thus likely to make the process completely regioselective. The proposed approach is shown in retrosynthetic form in Scheme 2.6. Thus, it was expected that the caged core **2.25** could be generated from diazo-group containing precursor **2.26** through rhodium- or copper-catalysed decomposition of the diazocarbonyl subunit. Compound **2.26** would, in turn, be generated through reaction of aldehyde **2.6** with succinic anhydride, or through Wittig olefination with 2-(triphenylphosphoranylidene)succinic anhydride and then, in each instance,

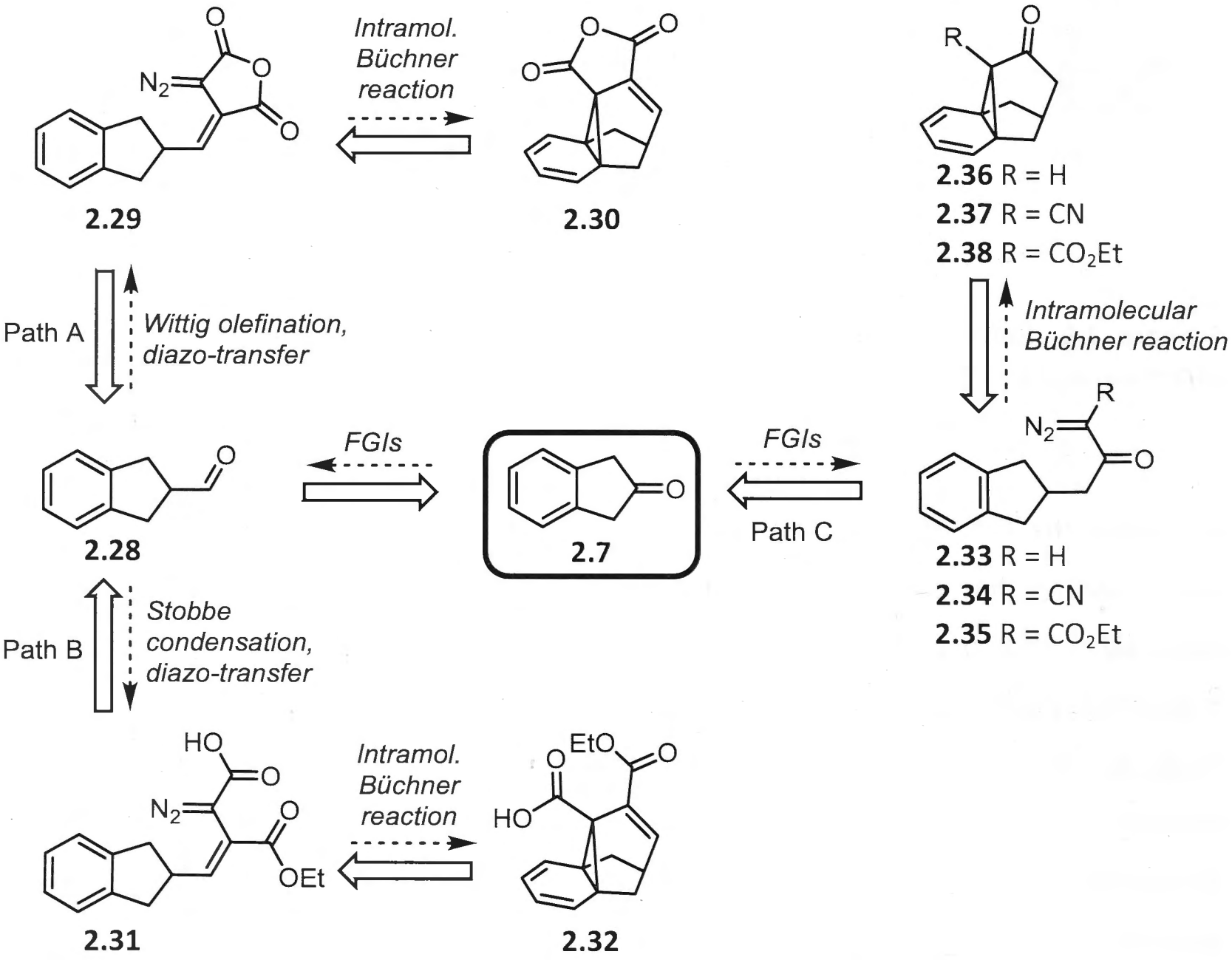
a diazo-transfer process. The precursor to aldehyde **2.6**, namely ketone **2.27**, would be derived, using standard chemistries, from commercially available 2-indanone (**2.7**).



Scheme 2.6. Retrosynthetic analysis of core structure **2.25** involving an intramolecular carbenoid addition approach.

At around the time this approach was being considered, Reisman *et al.*[10] published work demonstrating that a relevant cyclopropane can also be formed by addition of a metal-stabilised carbene to a pendant aromatic ring, *i.e.* by using a Büchner reaction (see Chapter 1). Since this method would allow the formation of the required diazocompounds in fewer steps, while the selectivity of the carbenoid addition should essentially remain the same, the possibility of assembling the [4.3.1]propelladiene core of salvileucalin B (**1.3**) using an intramolecular Büchner reaction was considered. Several variations on this theme are presented in Scheme 2.7. Thus, Path A involves subjection of aldehyde **2.28** to a Wittig olefination reaction and then a diazo-transfer process to give the succinic anhydride **2.29** which, following a Büchner reaction, should afford compound **2.30** incorporating the alkene associated with the developing α-methylene-γ-butyrolactone in the desired position. Similarly, Stobbe condensation[11] of aldehyde **2.28** (Path B) followed by a diazo-transfer reaction would give the monoester **2.31** and again establish the C-C double bond in the desired position prior to the arene cyclopropanation event. Of course, it is possible that this early stage incorporation of an alkene moiety would preclude the use of an intramolecular Büchner reaction because only that isomeric form of the substrate containing the *E*-configured double bond would be oriented in such a way as to allow for an intramolecular cyclopropanation reaction to occur. While the likely stereochemical outcome of the Stobbe condensation reaction was unclear, the Wittig reaction could be carried out using a stabilised phosphonium

ylide and thus be (more) likely to deliver the desired *E*-isomer as the major product.[12] Path C shows the less step-efficient option of forming the norcaradiene substructure through a Büchner reaction involving a simpler diazoketone substructure like those seen in compounds **2.33** - **2.35**. Methods for converting the ensuing functionality associated with the product cyclopropane into the desired lactone could then be explored once the propellane core was in place.

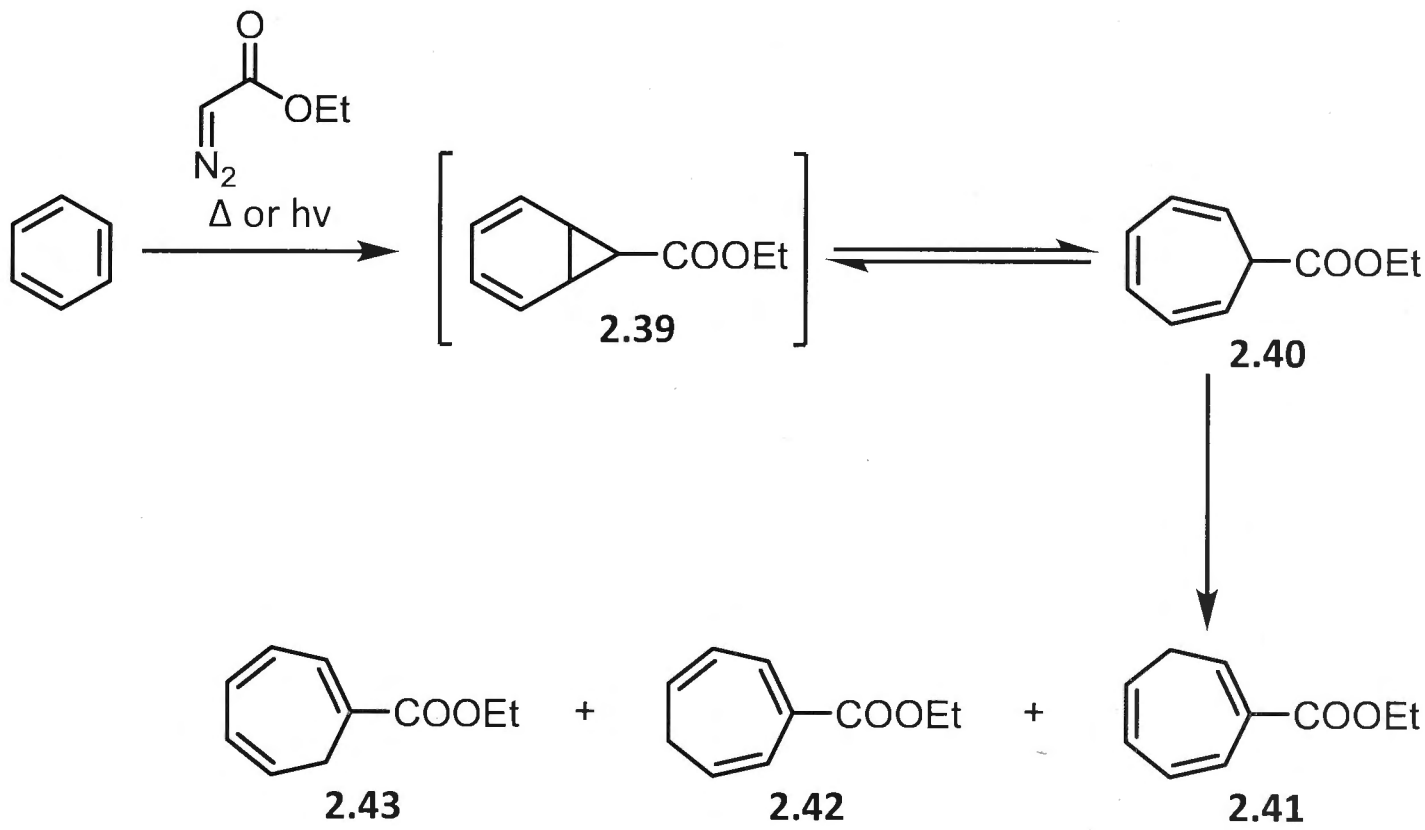


Scheme 2.7. The intramolecular Büchner reaction as an approach to the caged propellane core (as seen, for example, in compounds **2.36** - **2.38**) of salvileucalin B.

2.3.3. The Büchner Reaction and the Stability of the Resulting Products

The Büchner reaction is an important tool for the dearomatisation of benzenoid substrates and the formation of seven-membered rings or, in certain instances, their norcaradiene valence bond isomers. This reaction was discovered shortly after Curtius first synthesised ethyl diazoacetate from glycine in 1883.[13] Thus, when investigating the thermal decomposition of ethyl diazoacetate in benzene, Büchner isolated what appeared to be the norcaradiene **2.39** as a mixture with the three isomeric cycloheptatrienyl esters **2.41** - **43**

(Scheme 2.8).[14] According to Schenck,[15] under photochemical conditions the same reaction yielded the norcaradiene **2.39** as the exclusive product of reaction. When von Doering reinvestigated Büchner's original experiments more than 60 years later he found that the reaction yielded four cycloheptatrienyl esters (*viz.* compounds **2.40** - **2.43**) and thus suggesting that Büchner had not actually isolated norcaradiene **2.39**.[16] However, the isolation of cycloheptatriene **2.40** implied the intermediacy of the norcaradiene precursor **2.39** that undergoes a spontaneous and thermally allowed disrotatory electrocyclic ring-opening to give the observed cycloheptatriene **2.40**. Prototropic shifts within the primary product **2.40** would then account for the formation of the isomeric compounds **2.41** - **2.43**.



Scheme 2.8. The Büchner reaction of ethyl diazoacetate with benzene. Formation of cycloheptatrienes **2.40** - **2.43**.

Norcaradienes and their corresponding ring-opened cycloheptatrienes often exist in dynamic equilibrium.[17] Due to the strain of the cyclopropane ring the cycloheptatriene form is usually favoured.[18] However, various structural factors (Figure 2.2) have been identified that increase the equilibrium concentration of the norcaradiene. Thus, this form (**2.44**) can be stabilised if, (a), one or both of the norcaradiene double bonds is/are incorporated within an aromatic ring (**2.46**),[19] (b), nitrogen atoms are incorporated in positions 3 and 4 (**2.47**),[20] (c), electron-withdrawing substituents are present at C7 (**2.48**),[21] (d), unfavourable steric effects are exerted at positions 1 and 6 in the cycloheptatrienyl form (the so-called 'bracket effect') (**2.49**),[22] and/or (e), the carbon atoms 1 and 6 are bridged by an additional five-membered ring (**2.50**).[23]

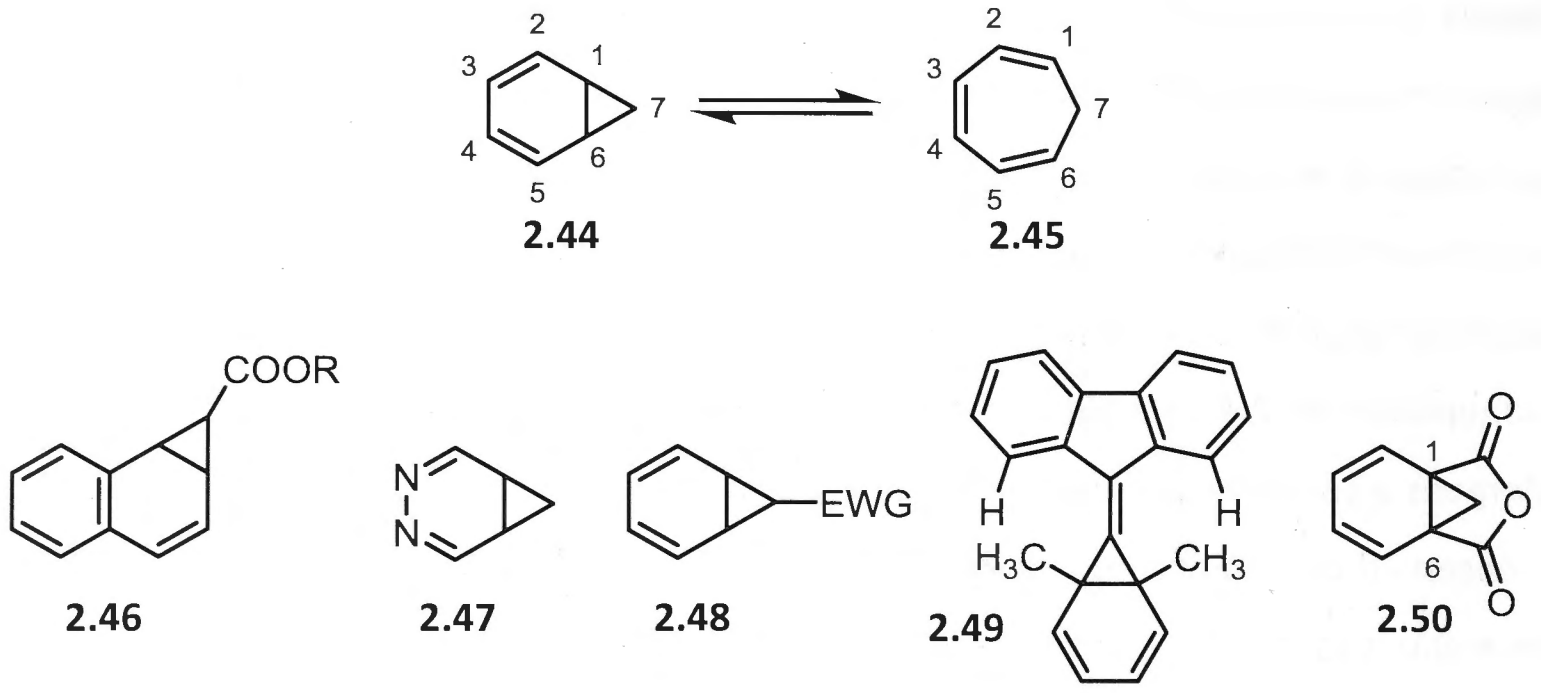


Figure 2.2. Substituents and other features favouring the norcaradiene valence isomer in the norcaradiene-cycloheptatriene equilibrium.

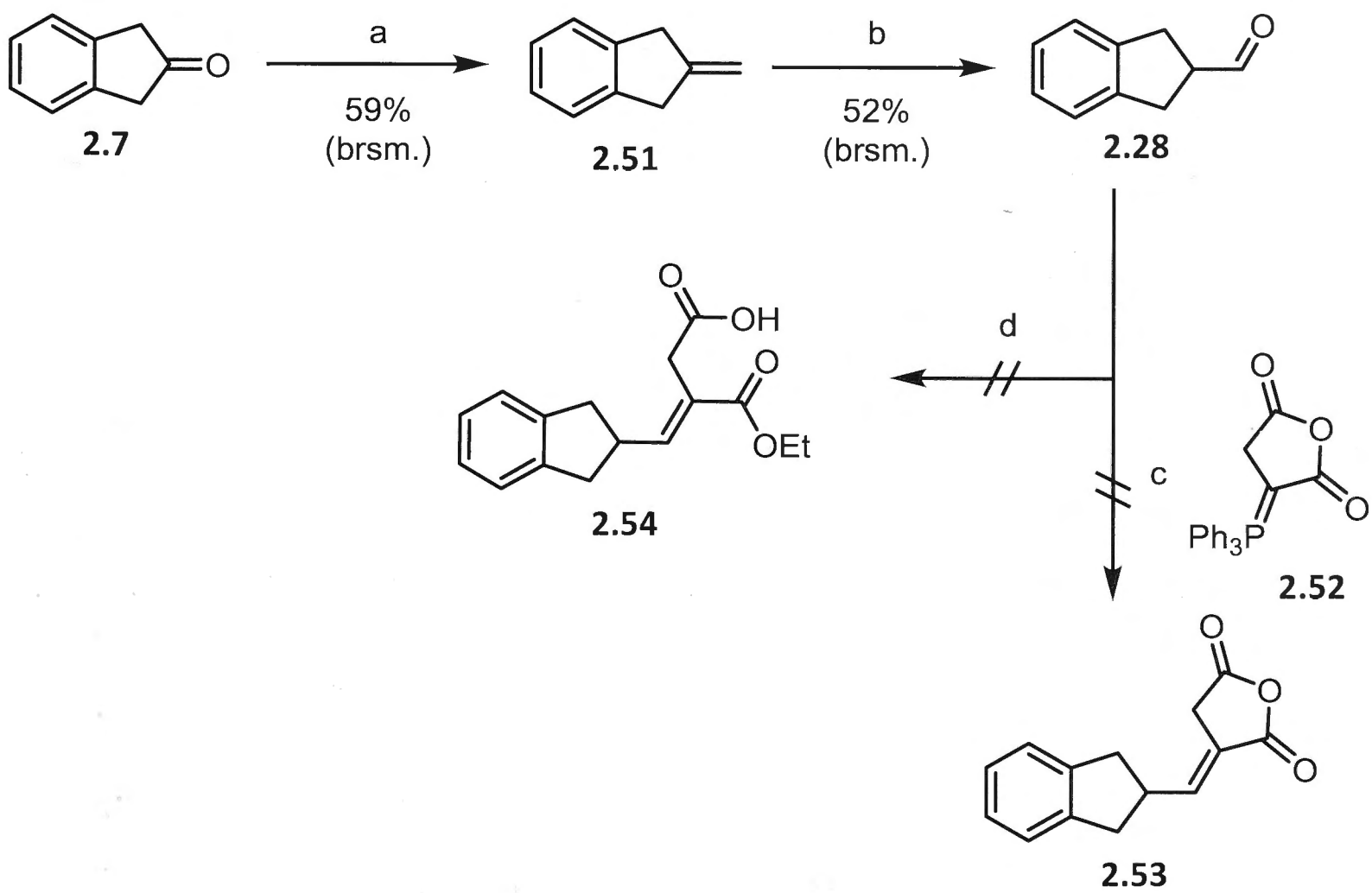
The stability of norcaradienes such as compound **2.50** provided an important precedent for the expectation that [4.3.1]propelladienes **2.30**, **2.32** and **2.36** - **2.38** could be formed by an intramolecular Büchner reaction and exist as such. The stability of compound **2.50** derives from the steric strain imposed by the bridging anhydride moiety on the corresponding ring-opened cycloheptatriene, a manifestation of Bredt's rule.*, [24]

2.3.4. Synthesis of Precursors and [4.3.1]Propelladiene 2.36

In an effort to prepare aldehydes **2.28** and **2.6** the precursor ketones **2.7** and **2.27**, were subjected to reaction with the ylid derived by treating (methoxymethyl)-triphenylphosphonium chloride with *s*-BuLi. However, neither of these reactions was successful. As an alternative, a Lombardo methylenation[25] was attempted (Scheme 2.9). Thus, a slurry of titanium tetrachloride, zinc and dibromomethane, which had been stirred at 5 °C for 20 h, was treated with 2-indanone (**2.7**) and so providing the desired product **2.51** in 59% yield (brsm). Attempts to improve this outcome by adding more of the Lombardo reagent or extending the reaction time failed. Instead, these measures resulted in decomposition of the starting material. Attempts to affect the Lombardo methylenation of ketone **2.27** also failed with only decomposition of the starting material being observed.

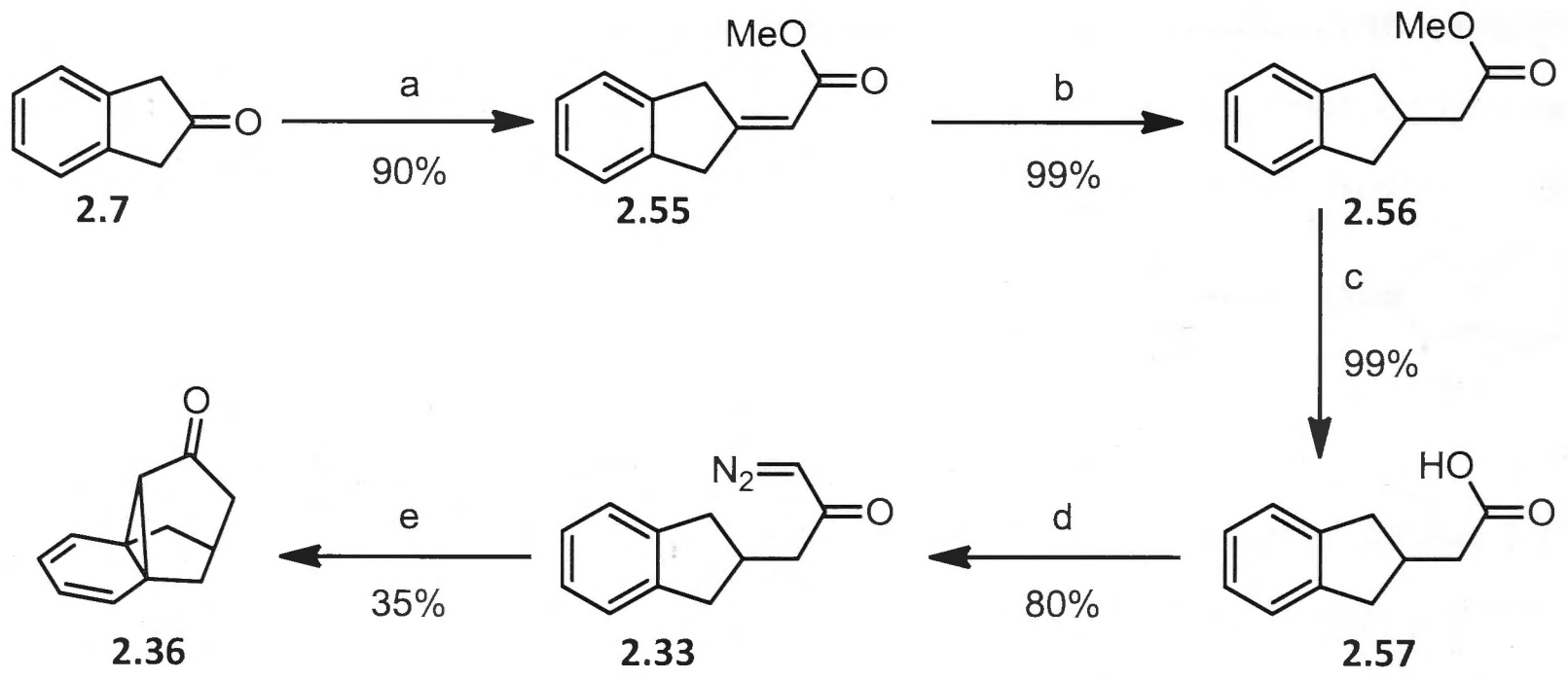
* Bredt's rule is an empirical rule originally stating that a C-C double bond cannot be placed at the branching positions of a carbon bridge. Since its original formulation, numerous so-called *anti*-Bredt molecules have been reported and the rule has thus been modified to state that in bi-(poly-)cyclic ring systems smaller than cyclooctane only a geometrically distorted C-C double bond of lower binding energy can be placed at a bridgehead position.

The methylenated compound **2.51** was subjected to a one-pot hydroboration/oxidation sequence[26] using borane dimethyl sulfide-complex followed by addition of NMO and TPAP.[27] By such means the desired aldehyde **2.28** was obtained in 52% yield (brsm). With this aldehyde in hand, the next task was to install functionality that could be elaborated into the diazo-function as well as the lactone. Work by Balasubramaniyan *et al.*[28] indicated that triphenylphosphonium succinic anhydride (**2.52**) was too unreactive to undergo olefination at around 70 to 80 °C, temperatures at which Wittig reagents normally readily reacted. Accordingly, and in an attempt to obtain anhydride **2.53**, the reaction was carried out using more forcing conditions *i.e.* at high pressure (19 kbar) for 14 - 24 h (Scheme 2.9). While a relevant molecular ion was detected in the GC-MS spectrum derived from the crude reaction mixture only dark-purple multi-component oils were observed. In another approach, aldehyde **2.28** was subjected to Stobbe condensation conditions,[11] with the intention of forming monoester **2.54** (Scheme 2.9). However, none of the desired product was isolated from what was a rather complex reaction mixture. Since neither of these reactions showed much promise the associated pathways depicted in Scheme 2.6 were abandoned.



Scheme 2.9. *Reagents and Conditions:* (a) $TiCl_4$-Zn-CH_2Br_2, THF/DCM, −40 °C to rt, 20 h; (b) BH_3•Me_2S, then NMO, TPAP, 4 Å molsieves; (c) **2.52**, DCM, 19 kbar, up to 45 h; (d) diethyl succinate, various bases, rt to 65 °C.

The pursuit of Path C (Scheme 2.7) was investigated as an alternative to the unsuccessful Wittig and Stobbe-based approaches detailed immediately above. In the first instance a readily accessible substrate was sought for the purpose of optimising the reaction conditions for the intramolecular Büchner reaction. The synthetic route ultimately identified for the assembly of the core propelladiene **2.36** is shown in Scheme 2.10. Specifically, 2-indanone (**2.7**) was subjected to a Horner-Wadsworth-Emmons reaction[29] with the anion derived from trimethyl phosphonoacetate. Hydrogenation of the resulting unsaturated ester **2.55** (90%) in the presence of 10% palladium on charcoal then yielded the desired methyl ester **2.56** in near quantitative yield. Saponification of the latter compound gave the corresponding acid **2.57** (99%) that was itself converted into the corresponding acid chloride and which was, in turn, treated with a freshly distilled solution of diazomethane in diethyl ether[30] and so providing the diazoketone **2.33** in 71% yield over four steps.



2.7 **2.55** **2.56** **2.57** **2.33** **2.36**

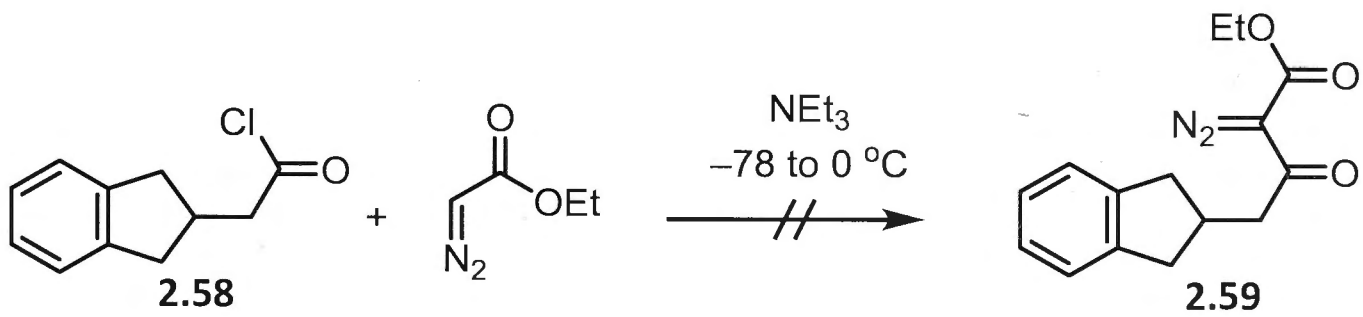
Scheme 2.10. *Reagents and Conditions:* (a) trimethyl phosphonoacetate, NaH, THF, 0 °C to rt, 22 h; (b) H_2 (1 or 3.4 bar), Parr-hydrogenator, 10% Pd-C (5 mol%), EtOAc, rt, 1 h; (c) NaOH, MeOH:H_2O (ratio 2:1), reflux, 1.5 h; (d) $(COCl)_2$, DMF, DCM, rt, 1.5 h, then CH_2N_2, Et_2O, 0 °C; (e) $Cu(acac)_2$, μ-wave, DCM, 120 °C, 2 min.

As the first step in seeking to establish the best reaction conditions for the intramolecular Büchner reaction, diazoketone **2.33** was subjected to microwave heating at 100 °C for one, two and five minutes in the presence of $Cu(acac)_2$. The optimum reaction time proved to be two minutes, with shorter ones giving incomplete conversion of the starting material and longer ones resulting in an increase in the presence of decomposition products. In addition to $Cu(acac)_2$ other catalysts were screened including $Cu(OAc)_2$, $Cu(OTf)_2$, Cu bronze, $Pd(OAc)_2$, $Co(OAc)_2$, $Co(acac)_2$ and $Rh_2(OAc)_4$. The arene cyclopropanation occurred very readily so that

even the use of $CuSO_4 \bullet H_2O$ resulted in complete consumption of the starting material after two minutes and yielded the desired [4.3.1]propelladiene **2.36** as colourless crystals. Thin layer chromatographic analysis of the crude reaction mixtures suggested that the cleanest reactions were obtained using $Cu(acac)_2$, $Cu(OTf)_2$ or $Co(OAc)_2$.

2.3.5. Construction of the Lactone-Fused Core of Salvileucalin B

Since the propelladiene **2.36** obtained as described above cannot easily be functionalized at the apical cyclopropyl carbon, it was necessary to include relevant functional groups at this position from the outset (Path C, Scheme 2.7). To such ends, the commonly used procedure for attaching a diazoalkane or similar compound to an acid chloride[31] was investigated. Thus, acid chloride **2.58**, obtained from reaction of acid **2.57** with oxalyl chloride and catalytic amounts of DMF, was treated with ethyl diazoacetate in an attempt to form diazo-compound **2.59**. Unfortunately, and despite many variations in temperature ranging from −78 °C to room temperature as well as the addition or omission of triethylamine, the desired reaction failed to take place. Thus, under no circumstances was any evidence for the formation of compound **2.59** obtained.



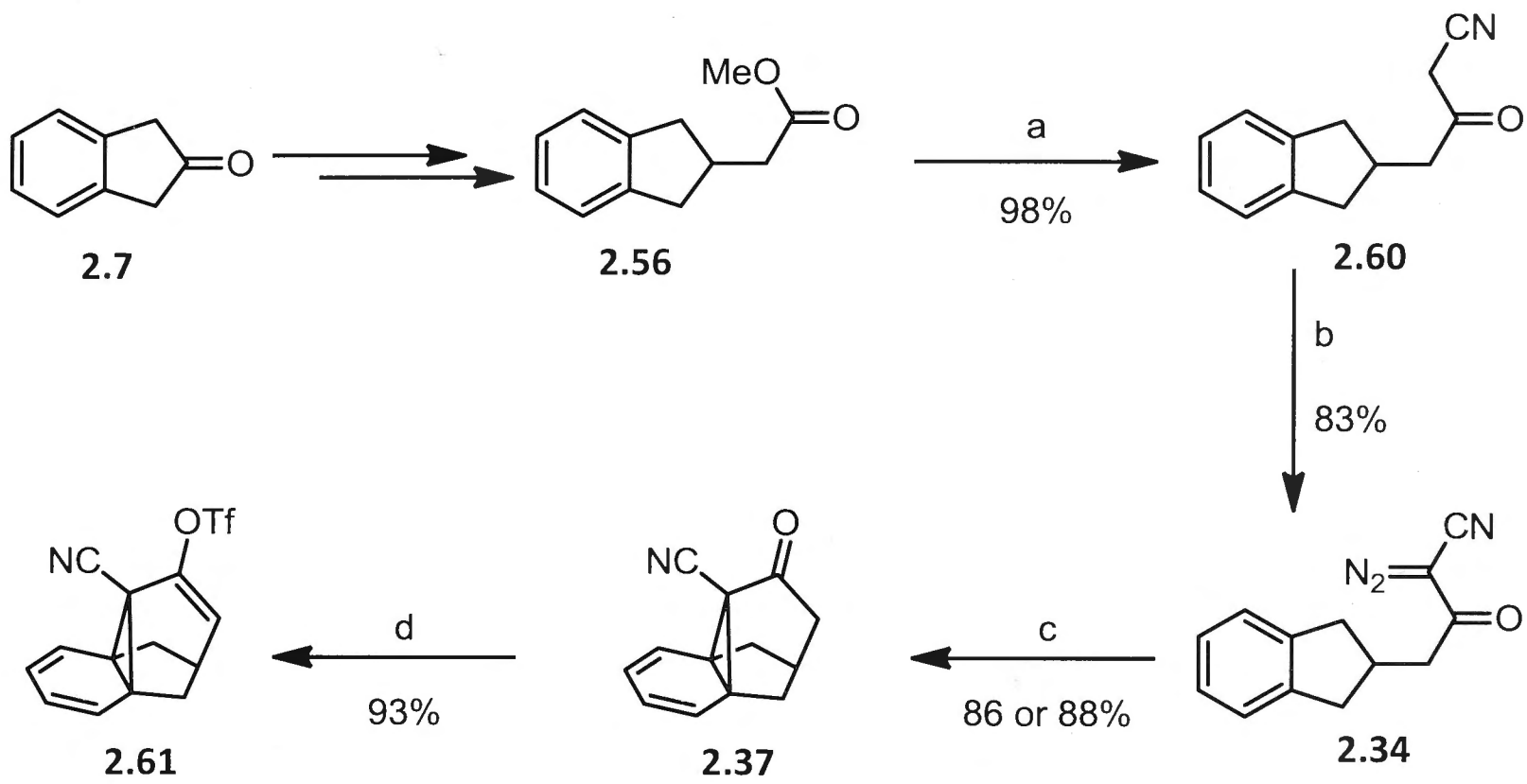
Scheme 2.11. Attempted synthesis of the non-terminal diazocarbonyl **2.59** using various conditions.

At this stage another, more promising approach to appropriately functionalised propelladienes was identified. This focused on the incorporation of smaller substituents that would exert few untoward steric effects during the course of the Büchner reaction. Specifically, then, Scheme 2.12 shows how the desired propellane core could be synthesised efficiently with a nitrile group attached at the apex of the cyclopropane and thus allowing for further elaboration at this position. So, nucleophilic substitution of ester **2.56** with the anion derived from acetonitrile[32] at −78 °C gave β-ketonitrile **2.60** in quantitative yield if the reaction was carried out using less than 200 mg of starting material. At larger scale, for example using 400 mg of starting material, the reaction did not go to completion as a result of competitive dimerisation

of the acetonitrile under the basic reaction conditions. This dimerisation is most likely caused by inefficient mixing and a resulting increase in reaction temperature (above the seemingly optimal one of −78 °C). The next step required a diazo-transfer reaction to form the diazo-substituted β-ketonitrile **2.34**. This was achieved by subjecting compound **2.60** to reaction with imidazolsulfonyl azide[33] in the presence of pyridine at 40 °C. This particular azide was originally alleged to be a safer and easier-to-handle alternative to the traditionally employed trifluoromethanesulfonyl azide since it is reputed to be stable to prolonged heating up to 80 °C and can be stored for extended periods of time as the hydrochloride salt. However, subsequent investigations into its stability[34] revealed its explosive nature and thus deterred us from attempting to store it in salt form. Indeed, the reagent was always used immediately after preparation and purification. The diazo-transfer reaction gave compound **2.34** in 83% yield. Interestingly, the use of bases other than pyridine resulted in the formation of a complex mixture from which none of the desired diazo-compound could be isolated.

Initially, the diazo-β-ketonitrile **2.34** was subjected to the Büchner reaction using the same conditions of microwave irradiation that were used earlier for the preparation of compound **2.37**. As a result it became clear that while the same reaction time and temperature were suitable for use in the present case different catalysts were necessary for effecting the arene cyclopropanation of this substrate. Catalysts that were screened included $Cu(acac)_2$, $Cu(tfacac)_2$, Cu bronze, $Rh_2(OAc)_4$ and $Rh_2(tfa)_4$. Whereas Cu bronze had given a relatively clean reaction with the model system **2.33**, it did not promote any reaction of diazo-β-ketonitrile **2.34**. Similarly, arene cyclopropanation of compound **2.34** in the presence of $Cu(acac)_2$ and $Cu(tfacac)_2$ did not go to completion, even when the catalyst loading was increased to 40 mol%. When the rhodium-based catalysts were used at a loading of 5 - 10 mol% in DCM then gas evolution was observed at room temperature but the reaction took over 2 h to go to completion. In contrast, at 100 °C in the microwave the intramolecular arene cyclopropanation reaction proceeded to completion after just 2 min. Reaction with $Rh_2(OAc)_4$ proceeded without formation of isolable byproducts and gave the desired caged core compound **2.37** in 88% yield. When $Rh_2(tfa)_4$ was used as catalyst then a byproduct, most likely resulting from a C-H insertion process, was formed. When the arene cyclopropanation was repeated under conditions where the concentration of diazocompound **2.34** was higher than 0.02 M, then formation of the same byproduct was also observed when using $Rh_2(OAc)_4$. To allow for the reaction to be carried out on a larger scale the use of "slow-addition" conditions was explored. Thus, a solution of diazo-β-ketonitrile **2.34** was added, *via* syringe pump, to a refluxing solution of $Rh_2(OAc)_4$ in DCM and such that the concentration of the diazocompound in the reaction mixture did not exceed 0.05 M at any time. Under such conditions propelladiene **2.37** was

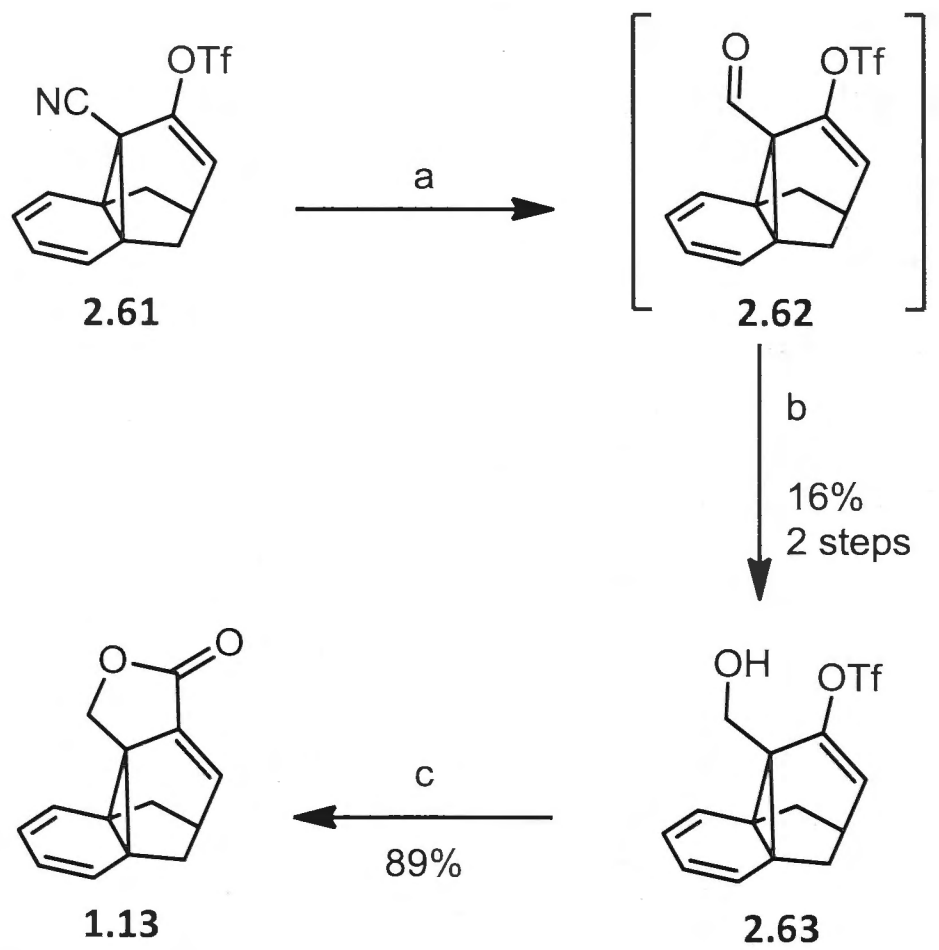
formed smoothly and ultimately obtained in 86% yield as a colourless, crystalline solid. As such its structure could be confirmed by single-crystal X-ray analysis (see Appendix 2 for details).



Scheme 2.12. *Reagents and Conditions*: (a) MeCN, LiHMDS, THF, −78 °C, 1 h; (b) imidazole sulfonyl azide, pyridine, MeCN, 40 °C, 14 h; (c) $Rh_2(OAc)_4$, μwave, 2 min, DCM, 100 °C, 88% or $Rh_2(OAc)_4$, DCM, 40 °C, 2 h, slow addition, 86%; (d) $PhNTf_2$, LiHMDS, THF, −78 °C, 1 h.

As the first step in its further elaboration, propelladiene **2.37** was subjected to reaction with LiHMDS and *N*-phenyltriflimide at −78 °C and this resulted in formation of the enol triflate **2.61** (93%). The next elements in the synthesis included the two-step reduction of the nitrile group of enol triflate **2.61**. Thus, treatment of this compound with DIBAL-H was expected to afford the corresponding aldehyde in the first instance and this was to be followed by a second reduction to provide the desired alcohol, the substrate required for the projected carbonylative coupling that would lead to the targeted (northern) lactone. Accordingly, enol triflate **2.61** was subjected to reaction with DIBAL-H at −40 °C for 1 h, followed by aqueous acidic workup using HCl.[†] Resubjecting the material so obtained to a second DIBAL-H reduction step yielded the anticipated alcohol **2.63** in 16% yield over two steps. The second reduction step was carried out at −78 °C for convenience but the yield was essentially found to be the same when the reaction was carried out at −40 °C. Because the yield of alcohol **2.63** resulting from these two consecutive DIBAL-H reductions was consistently low, efforts were made to use the more stable nonaflate group. However, in this case the DIBAL-H reduction yielded an unexpected byproduct (see Chapter 3) that could not be used for the present purposes.

[†] The product (**2.62**) of this reaction underwent a rearrangement which most likely included a [3,5]-sigmatropic rearrangement process (see Chapter 3 for details).



Scheme 2.13. *Reagents and Conditions:* (a) DIBAL-H, DCM, –40 °C, 1 h, HCl-workup; (b) DIBAL-H, DCM, –78 °C, 1 h, HCl-workup; (c) CO, $Pd(PPh_3)_4$, NEt_3, LiCl, THF, rt, 2 h.

Palladium-catalysed carbonylative coupling[35] of alcohol **2.63** and subsequent spontaneous lactonisation resulted in the formation of the by now long sought-after compound **1.13** which was obtained in 89% yield. Thus, in what is a protecting group-free synthesis, the caged core lactone **1.13**, a *meso*-compound that embodies the main substructure of the target natural product, had been generated in nine steps and 8% overall yield from commercially available 2-indanone (**2.7**).[‡]

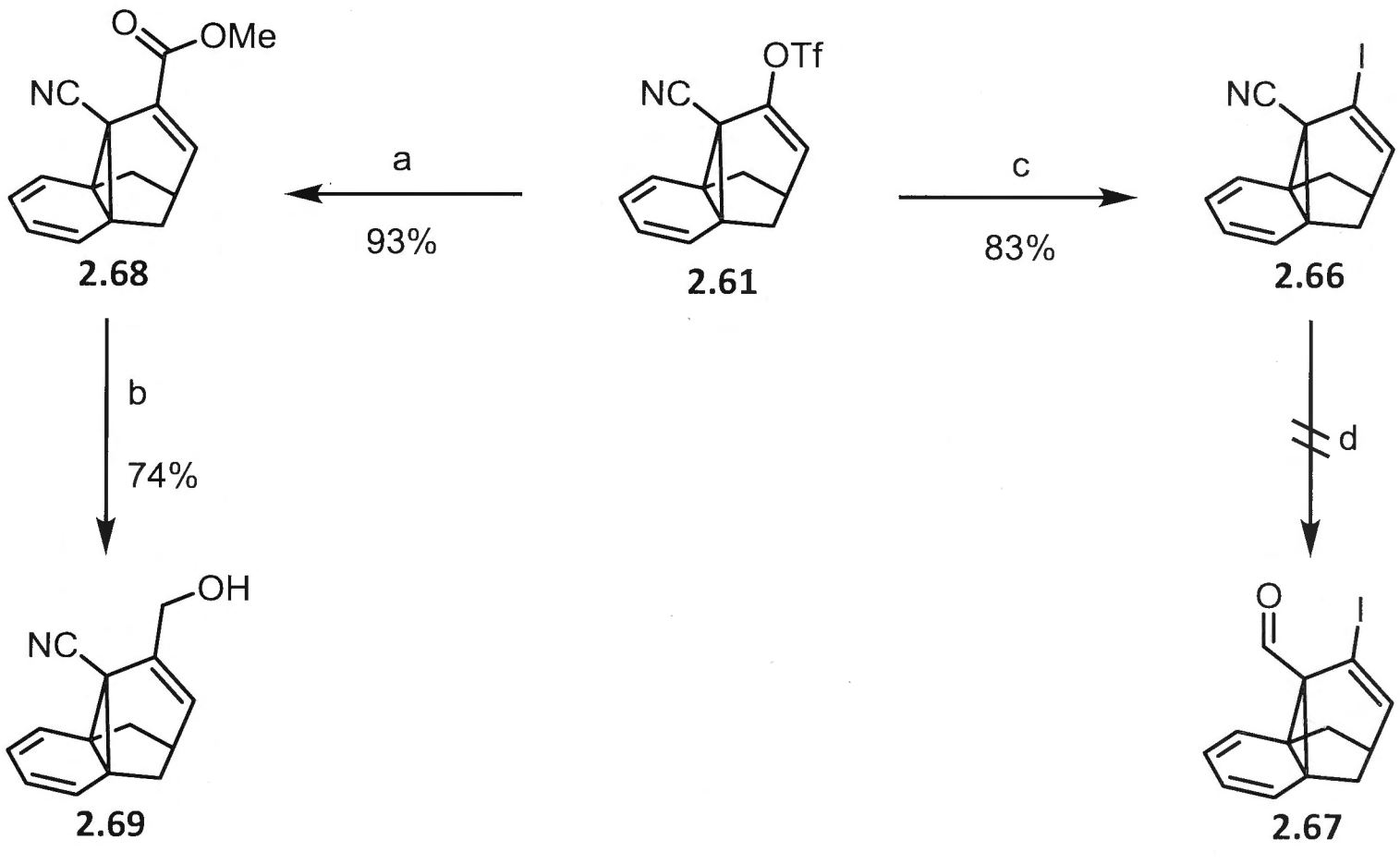
2.4. Exploring Alternatives to the Inefficient DIBAL-H Reduction of Nitrile 2.61

The successful acquisition of the core structure, **1.13**, of the target natural product prompted efforts to improve the efficiency of the sequence that suffered from a low-yielding reduction step involving nitrile **2.61**. Efforts to improve this situation involved exploring the use of other reduction methods as well as different synthetic pathways.

In order to establish if the enol triflate moiety within compound **2.61** was unstable to the DIBAL-H reduction conditions this was converted, by standard methods, into iodide **2.66** (83%) which was then subjected to the usual DIBAL-H reduction conditions as shown in Scheme 2.14. However, these changes gave rise to a complex mixture of products and none of the characteristic resonances due to an aldehyde or the rearranged product (arising from a [3,5]-

[‡] These and other results were presented by the author at the RACI NSW Organic Chemistry Group One-Day Symposium in Wollongong, Australia, on 1 December 2010, while the first enantioselective total synthesis of salvileucalin B by the Reisman group at CalTech was published online on 21 December 2010.

sigmatropic rearrangement as discussed in Chapter 3) were observed in the ^{1}H NMR spectrum of the crude reaction mixture. DIBAL-H reduction of the nitrile function within compound **2.68** that had been generated through carbonylative coupling of triflate **2.61** in the presence of methanol was also unsuccessful with only the associated ester function being reduced to give the primary alcohol **2.69** (74%).

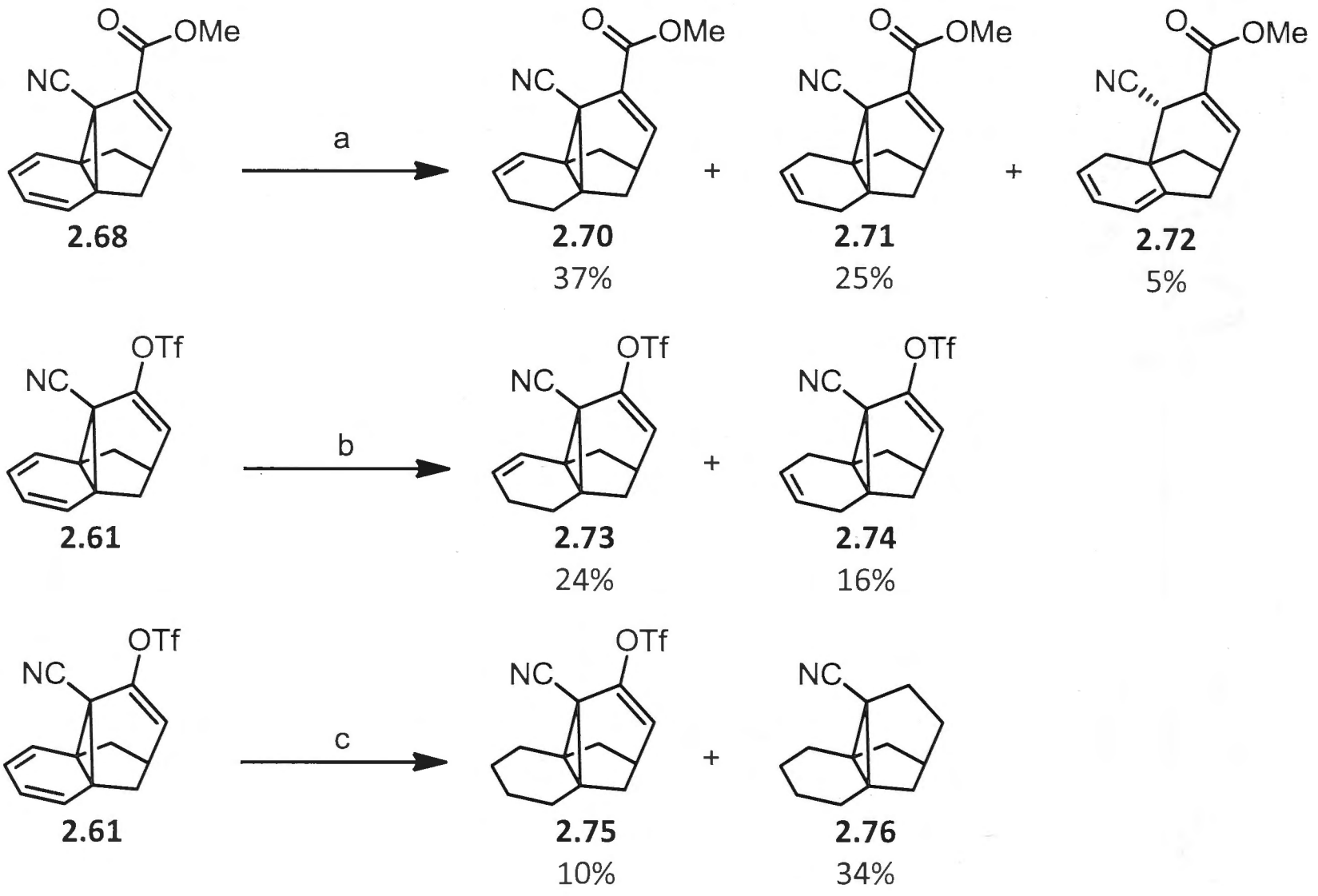


Scheme 2.14. *Reagents and Conditions*: (a) CO (1 atm), $Pd(PPh_3)_4$, NEt_3, MeOH, rt, 3 h; (b) DIBAL-H (2 eq.), DCM, −40 °C, 1 h, HCl-workup; (c) $Pd(PPh_3)_4$, LiCl, $(SnMe_3)_2$, NIS, THF, 60 °C to rt, 14 h; (d) DIBAL-H, DCM, −40 °C, 1 h, HCl-workup.

To test if any other reagents were capable of effecting a high-yielding reduction of the nitrile group within compound **2.61** or the derived ester **2.68**, and because of its extensive and successful use in the Banwell Research Group,[32b,36] the effects of Raney-cobalt and hydrogen gas were investigated. However, subjection of each of these substrates to the reaction conditions specified in Scheme 2.15 resulted in hydrogenation of the C-C double bonds and, in some cases, hydrogenolysis of the cyclopropane ring.[37] Despite previous observations within the Banwell Group that Raney-cobalt preferentially reduces nitriles in the presence of C-C double bonds,[36c] the nitrile function of both starting materials remained intact in the present cases.

While the Raney-cobalt mediated reactions just described resulted in 1,2- and 1,4-reductions of the diene moiety, as well as opening of the cyclopropane ring within compound **2.61** (Scheme 2.15), the reaction of the same substrate with hydrogen in the presence of palladium

on charcoal was even less selective and resulted in exhaustive hydrogenation, as well as cleavage of the triflate group. Frustratingly, the nitrile function remained intact in every instance.



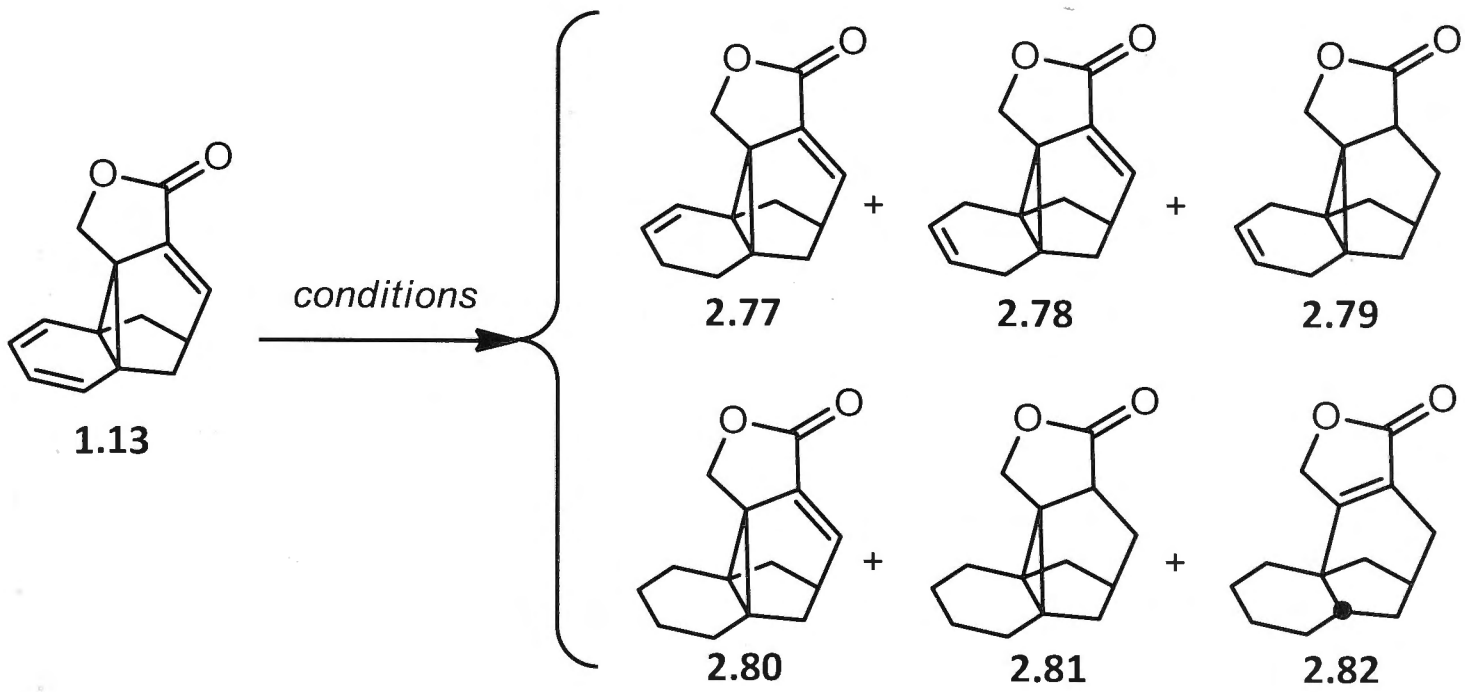
Scheme 2.15. *Reagents and Conditions*: (a) H_2 (1 atm), Raney-cobalt (*ca.* 200 mol%), MeOH/NH_3, rt, 4 h; (b) H_2 (1 atm), Raney-cobalt (*ca.* 200 mol%), MeOH/NH_3, rt, 2 h; (c) H_2 (1 atm), Pd-C (5 mol%), EtOAc, rt, 0.5 h.

While the nitrile group associated with compounds **2.61** and **2.68** could not be reduced under any of the reaction conditions specified in Scheme 2.15, these and related hydrogenation techniques did allow for the synthesis of partially hydrogenated analogues of the core lactone **1.13**. Specifically, when compound **1.13** was subjected to the three different reduction protocols shown in Scheme 2.16 and the associated Table 2.1 then the partially hydrogenated compounds **2.77** - **2.82** were obtained. The Raney-cobalt mediated reduction proceeded more slowly than the analogous rhodium- or palladium-catalysed processes and in this way the mono-hydrogenated species **2.77** and **2.78** could be isolated in roughly equal amounts after 3.5 h at room temperature and by using approximately 200 mol% of a slurry of Raney-cobalt in methanol. The only over-reduced product, **2.79**, arising from this reaction was that lacking the C-C double bond of the original α-methylene-γ-butyrolactone moiety. Presumably, this

compound arises from reduction of the *meso*-compound **2.78**. Interestingly, compound **2.79** was only ever isolated from the Raney-cobalt mediated reduction process.

The characteristic resonances of the olefinic hydrogens (multiplets at δ 6.0 and 5.8) associated with the unsymmetrical compound **2.77** could be seen in the ^{1}H NMR spectrum of the crude reaction mixture arising from the palladium-catalysed hydrogenation reaction. However, this product was formed in such small amounts that it could never be obtained in pure form. Both the palladium- and rhodium-catalysed hydrogenation reactions yielded over-reduced lactones **2.80** - **2.82** after only 0.25 to 0.5 h at room temperature. However, the rhodium-catalysed reaction seemed to be faster and not even traces of mono-hydrogenated material were observed. In contrast, during the palladium-catalysed reaction the 1,4-reduced lactone **2.78** was obtained in 42% yield.

In broad terms, then, the palladium- and rhodium-catalysed reduction processes effected more extensive reduction of substrate **1.13** than did those involving Raney-cobalt. The former catalysts also favoured selective reduction of the diene moiety, while the α,β-unsaturated lactone moiety was hydrogenated last. The Raney-cobalt catalyst favoured hydrogenation of only one of the double bonds of the diene, and then appeared to selectively reduce the double bond conjugated with the lactone moiety.



Scheme 2.16. Products arising from the metal-catalysed hydrogenation of compound **1.13**.

Table 2.1. Products **2.77** - **2.82** Arising from Hydrogenation of Core Lactone **1.13** in the Presence of Various Catalysts.

Catalyst	Conditions	Yields (%)					
		2.77	**2.78**	**2.79**	**2.80**	**2.81**	**2.82**
Raney-Cobalt	H_2, MeOH/NH_3, rt	50	40	5	-	-	-
Rh on Al_2O_3	H_2, EtOAc, rt	-	-	-	25	50	8
Pd on C	H_2, EtOAc, rt	-	42	-	8	16	33

2.5. Biological Testing[38]

Because of their structural resemblance to the caged-core substructure of the biologically active natural product salvileucalin B (**1.3**), compounds **1.13** and **2.77** - **2.82** were tested against the cell lines SW620, SW620 Ad300, KB-3-1, and KB-V1 which are, respectively, a human colon cancer cell line, a daughter cell line overexpressing P-gp (prepared by culturing SW620 in the presence of adriamycin), a human cervical cancer cell line, and a daughter cell line overexpressing P-gp (prepared by culturing KB-3-1 in the presence of vinblastine). P-gp is an ATP binding cassette (ABC) transporter protein that drives multi-drug resistance when tested in the SW620 cell line.

Even though four of the synthetic materials (**1.13**, **2.77**, **2.78** and **2.79**) tested embody an α-alkylidene-γ-butyrolactone residue they were not particularly cytotoxic as seen from the values given in **Table 2.2**. The origins of this slightly surprising situation are under investigation. In a separate set of evaluations to test whether or not compounds **1.13** and **2.77** - **2.82** possess any capacity to inhibit P-gp based multidrug resistance mechanisms displayed by numerous human cancer cell lines, they were subjected to a flow cytometry-based calcein AM assay. Once again, however, no significant activity was observed with all the compounds displaying calcein FAR (fluorescence arbitrary ratio) values in the range 0.54 to 0.71 as compared with the value of 43.5 measured for the positive control verapamil at the same concentration.

Table 2.2. Cytotoxicity Test Results for Compounds **1.13** and **2.77** - **2.82**.

Compound	IC_{50} (μM)				Calcein
	SW620	SW620 Ad300	KB-3-1	KB-V1	FAR
1.13	> 100	> 100	> 100	> 100	0.54
2.77	> 100	> 100	100	> 100	0.71
2.78	> 100	> 100	> 100	> 100	0.62
2.79	> 100	> 100	> 100	> 100	0.63
2.80	83	> 100	> 100	> 100	0.54
2.81	> 100	> 100	> 100	> 100	0.65
2.82	> 100	> 100	> 100	> 100	0.63

2.6. Conclusion

The intramolecular Büchner reaction has provided a highly effective means for assembling the [4.3.1]propellane substructure **1.13** associated with the cytotoxic target natural product salvileucalin B (**1.3**). Furthermore, reduction of the former compound under a variety of conditions has provided a series of partially or fully saturated derivatives, namely compounds **2.77** - **2.82**, that have been used to probe for the pharmacophore of the target natural product. The lack of cytotoxic effects displayed by compounds **1.13** and **2.77** - **2.82** suggests that the second lactone ring and the associated furan moiety incorporated within the natural product are contributing in a significant way to its biological properties. Accordingly, studies, as detailed in Chapter 5, were undertaken to find means by which the *meso*-compound **1.13** can be elaborated, using desymmetrising acylation, epoxidation and oxygenation protocols, so as to incorporate one or both of these residues and, thereby, deliver enantiomerically-enriched compounds displaying useful cytotoxic properties.

2.7. References

(1) a) Banwell, M.; Halton, B. *Aust. J. Chem.* **1979**, *32*, 2689; b) Banwell, M.; Halton, B. *Aust. J. Chem.* **1980**, *33*, 2673; c) Banwell, M. G.; Lambert, J. N.; Gravatt, G. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, *0*, 2817; d) Banwell, M. G.; Ma, X.; Taylor, R. M.; Willis, A. C. *Org. Lett.* **2006**, *8*, 4959; e) Bissember, A. C.; Phillis, A. T.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2007**, *9*, 5421.

(2) Birch, A. J.; Fitton, P.; Smith, D. C. C.; Steere, D. E.; Stelfox, A. R. *J. Chem. Soc.* **1963**, 2209.

(3) Vogel, E.; Biskup, M.; Vogel, A.; Haberland, U.; Eimer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 603.

(4) a) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44; b) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318; c) Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654.

(5) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1991**, *56*, 1027.

(6) a) Warner, P. M.; Herold, R. D. *J. Org. Chem.* **1983**, *48*, 5411; b) Warner, P. M.; Herold, R. D. *Tetrahedron Lett.* **1984**, *25*, 4897.

(7) a) Seebach, D.; Dammann, R.; Lindner, H. J.; Kitschke, B. *Helv. Chim. Acta* **1979**, *62*, 1143; b) Banwell, M. G.; Gravatt, G. L.; Rickard, C. E. F. *J. Chem. Soc., Chem. Commun.* **1985**, *0*, 514.

(8) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(9) Hussain, Z.; Koley, D.; Hopf, H. *Helv. Chim. Acta* **2005**, *88*, 3263.

(10) Levin, S.; Nani, R. R.; Reisman, S. E. *Org. Lett.* **2010**, *12*, 780.

(11) Stobbe, H. *Ber.* **1893**, *26*, 2312.

(12) a) Vedejs, E.; Peterson, M. J. In *Top. Stereochem.*; John Wiley & Sons, Inc.: 2007, p 1; b) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann. Chem.* **1997**, *7*, 1283; c) Röder, E.; Krauß, H. *Liebigs Ann. Chem.* **1992**, *3*, 177.

(13) Curtius, T. *Ber.* **1883**, *16*, 2230.

(14) Buchner, E.; Curtius, T. *Ber.* **1885**, *18*, 2377.

(15) Schenck, G. O.; Ziegler, H. *Liebigs Ann. Chem.* **1953**, *584*, 221.

(16) Von E. Doering, W.; Knox, L. H. *J. Am. Chem. Soc.* **1957**, *79*, 352.

(17) McNamara, O. A.; Maguire, A. R. *Tetrahedron* **2011**, *67*, 9.

(18) a) Maier, G. *Angew. Chem., Int. Ed.* **1967**, *6*, 402; b) Vogel, E.; Roth, H. D.; Wiedeman.W; Gunther, H.; Eimer, J. *Liebigs Ann. Chem.* **1972**, *759*, 1.

(19) Buchner, E.; Hediger, S. *Ber.* **1903**, *36*, 3502.

(20) a) Maier, G. *Chem. Ber.* **1962**, *95*, 611; b) Maier, G. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 621; c) Maier, G. *Chem. Ber.* **1965**, *98*, 2438; d) Maier, G. *Chem. Ber.* **1965**, *98*, 2446; e) Sauer, J.; Heinrichs, G. *Tetrahedron Lett.* **1966**, *7*, 4979.

(21) a) Hoffmann, R.; Stohrer, W. D. *J. Am. Chem. Soc.* **1971**, *93*, 6941; b) Wehner, R.; Guenther, H. *J. Am. Chem. Soc.* **1975**, *97*, 923; c) Balci, M.; Fischer, H.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 301; d) Clark, T.; Spitznagel, G. W.; Klose, R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1984**, *106*, 4412.

(22) Prinzbach, H.; Fischer, U.; Cruse, R. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 251.

(23) a) Darms, R.; Threlfall, T.; Pesaro, M.; Eschenmoser, A. *Helv. Chim. Acta* **1963**, *46*, 2893; b) Vogel, E.; Wiedemann, W.; Kiefer, H.; Harrison, W. F. *Tetrahedron Lett.* **1963**, *4*, 673; c) Vogel, E.; Maier, W.; Eimer, J. *Tetrahedron Lett.* **1966**, *7*, 655.

(24) a) Bredt, J. *Liebigs Ann. Chem.* **1924**, *437*, 1; b) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683.

(25) Lombardo, L. *Org. Synth.* **1993**, *8*.

(26) Yates, M. H. *Tetrahedron Lett.* **1997**, *38*, 2813.

(27) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(28) Balasubramaniyan, V.; Tongare, D. B.; Gosavi, S. S. *Proc. - Indian Acad. Sci., Chem. Sci.* **1993**, *105*, 265.

(29) Ksander, G. M.; deJesus, R.; Yuan, A.; Fink, C.; Moskal, M.; Carlson, E.; Kukkola, P.; Bilci, N.; Wallace, E.; Neubert, A.; Feldman, D.; Mogelesky, T.; Poirier, K.; Jeune, M.; Steele, R.; Wasvery, J.; Stephan, Z.; Cahill, E.; Webb, R.; Navarrete, A.; Lee, W.; Gibson, J.; Alexander, N.; Sharif, H.; Hospattankar, A. *J. Med. Chem.* **2001**, *44*, 4677.

(30) Vogel, A. *Vogel's Textbook of Practical Organic Chemistry*; 5 ed.; Longman, 1989.

(31) a) Doyle, M. P.; McKervey, A. M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998; b) Cuevas-Yañez, E.; Muchowski, J. M.; Cruz-Almanza, R. *Tetrahedron* **2004**, *60*, 1505.

(32) a) Puterová, Z.; Andicsová, A.; Végh, D. *Tetrahedron* **2008**, *64*, 11262; b) Jones, M. T.; Schwartz, B. D.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2009**, *11*, 3506.

(33) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797.

(34) a) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2011**, *13*, 2514; b) Fischer, N.; Goddard-Borger, E. D.; Greiner, R.; Klapötke, T. M.; Skelton, B. W.; Stierstorfer, J. *J. Org. Chem.* **2012**, *77*, 1760.

(35) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972.

(36) a) Schwartz, B. D.; White, L. V.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2011**, *76*, 8560; b) White, L. V.; Schwartz, B. D.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2011**, *76*, 6250; c) Reekie, T. A.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2012**, *77*, 10773; d) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14*, 5621.

(37) a) Wuesthoff, M. T.; Rickborn, B. *J. Org. Chem.* **1968**, *33*, 1311; b) Zutterman, F.; Krief, A. *J. Org. Chem.* **1983**, *48*, 1135.

(38) Heinrich, N.; Banwell, M. G.; Willis, A. C.; Cade, I. A.; Capon, R. J.; Huang, X.-C. *Aust. J. Chem.* **2012**, *65*, 1679.

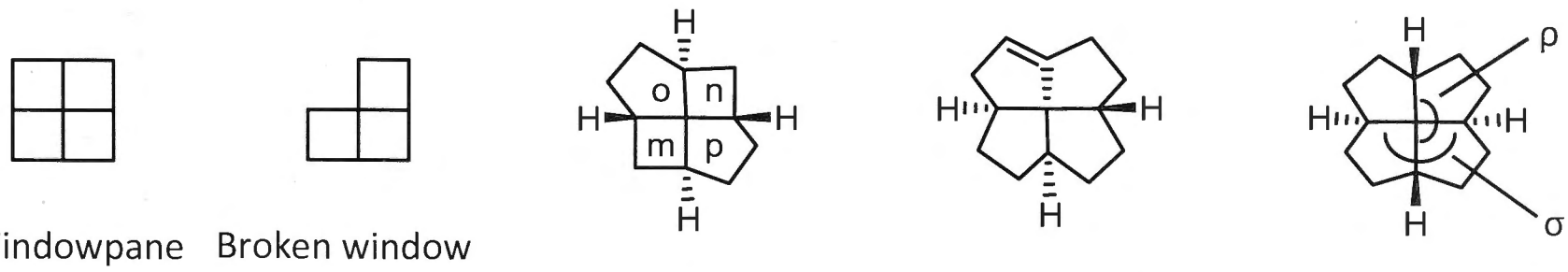
Chapter 3

The Interconversion of Certain Propelladienes and Fenestratrienes

3.1. Introduction

3.1.1. Nomenclature and Structural Characteristics of Fenestranes

The term 'fenestrane'[1] was originally assigned to the as yet unsynthesised compound **3.1** (Figure 3.1) due to its obvious similarity to a window (Latin - fenestra). When applying the usual system for naming polycyclic frameworks, this compound is called tetracyclo[3.3.1.$0^{3,9}$.$0^{7,9}$]nonane, but the simplified name [4.4.4.4]fenestrane is clearly more descriptive (and even, perhaps, convenient). This terminology has since been expanded to cover all compounds incorporating a central quaternary carbon that serves as a common vertex for four mutually fused carbocycles. It also serves to describe the related tricyclic or "broken window" systems such as [4.4.4]fenestrane **3.2**.



Windowpane or [4.4.4.4]-fenestrane **3.1**

Broken window or [4.4.4]-fenestrane **3.2**

c,c,c,c-[4.4.5.5]-fenestrane **3.3**

α,α,β-[5.5.5.5]-fenestrane **3.4**

c,c,c,c-[5.5.5.5]-fenestrane **3.5**

Figure 3.1. Representative fenestranes and the nomenclature used to define them.

The following terminology[1c] has been introduced to better define the characteristics of fenestranes:

- An [m.n.o.p]fenestrane is specified by the size of the four rings with m < n < o < p. (**3.3**)

- Stereoisomeric fenestranes are described by the number of *cis*- (*c*-) and *trans*- (*t*-) bicyclo[x.y.0]alkane subunits (**3.3** - **3.5**) present within a given molecular framework. Alternately, the letters α and β are used to describe ring-junction substituents below and above, respectively, the plane defined by the Fischer projection (**3.4**). Both methods begin by defining the uppermost ring-junction substituent.
- The bond angles that are used to "measure" the widening or planarising distortion of the central $C(C_4)$ substructure are defined as ρ and σ, respectively, as shown in structure **3.5**.

A modified and more commonly used[2] fenestrane nomenclature that has been adopted herein as seen, for example, in Table 3.1 on page 49, identifies the smallest of the rings present and progresses clockwise, allowing the connectivity of the four fused carbocycles to become apparent, if these are of different size. Thus, [4.4.5.5]fenestrane **3.3** becomes [4.5.4.5]fenestrane when this slightly more explicit nomenclature is employed.

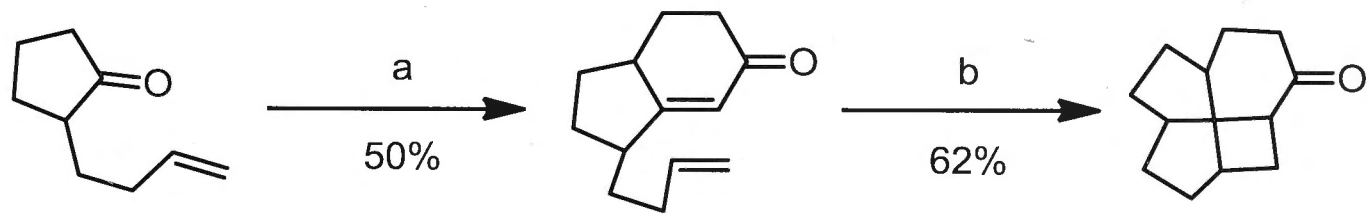
The widespread interest in the synthesis of fenestranes and related compounds follows from the possibilities of severely distorting the geometry of the central carbon atom from a normal tetrahedral arrangement (C-C-C = 109.5°) and, ultimately (at least from a theoretical standpoint), creating a flat/planar tetracoordinate carbon.[1a,1e] Several crystalline fenestranes have now been prepared and, in some cases, the resulting X-ray analyses have revealed remarkable deviations from the idealised tetrahedral geometry.[1b,1c,1f,2-3] However, most hydrocarbon fenestranes are not crystalline and, therefore, theoretical methods have had to be employed in order to gauge the attendant distortions. Semi-empirical calculations by Keese and Thommen[1c] identified several factors that can influence the extent of such distortions. Specifically, then, the incorporation of small rings, the presence of *trans*-fused bicyclo[x.y.0]alkane subunits and/or ring-junction double bonds as well as the nature of certain ring-junction substituents can have a significant impact. It is self-evident that incorporation of smaller ring-sizes increases the planarising distortion. Even though windowpane **3.1** - the ultimate but as yet unrealised target of most of these studies - has been much discussed on a theoretical level,[1a-c,1e,4] the synthetic endeavours of incorporating small rings in a fenestrane are limited by the ring- and angle-strain within the developing frameworks. The smallest fenestrane synthesised to date is made up of an all-*cis* fused [4.4.4.5]fenestrane core.[4b]

3.1.2. Key Syntheses

In the early phases of studies on the synthesis of fenestranes, photochemically-promoted [2+2]-cycloaddition reactions were amongst the most popular/effective methods used for introducing four-membered rings into the target frameworks.[4b,5] Since then, new methods have emerged, some building on the photocycloaddition method to make all-*cis* fenestranes,[5] while others use entirely different approaches to incorporate *trans*-bicyclo[x.y.0]alkane units.[1f,2-3,6] An overview of the impact of incorporating these various structural features into certain representative fenestranes is given in Section 3.1.3.

Progress Towards all-*cis* [4.4.4.4]Fenestrane

The first fenestrane[5a] was made in 1972 by Georgian and Saltzmann, who also named this family of compounds. Thus, the cyclopentanone derivative **3.6** was converted, using Robinson annulation protocols, into diene **3.7** that, upon photolysis, underwent an intramolecular [2+2]-cycloaddition reaction to give [4.5.5.6]fenestrane **3.8** (Scheme 3.1) and thereby introducing the final two rings in a single step. Because the resulting all-*cis* fused [4.5.5.6]fenestrane **3.8** was not crystalline the measurement of the relevant bond angles (so as to determine the distortion about the central carbon) could not be undertaken.

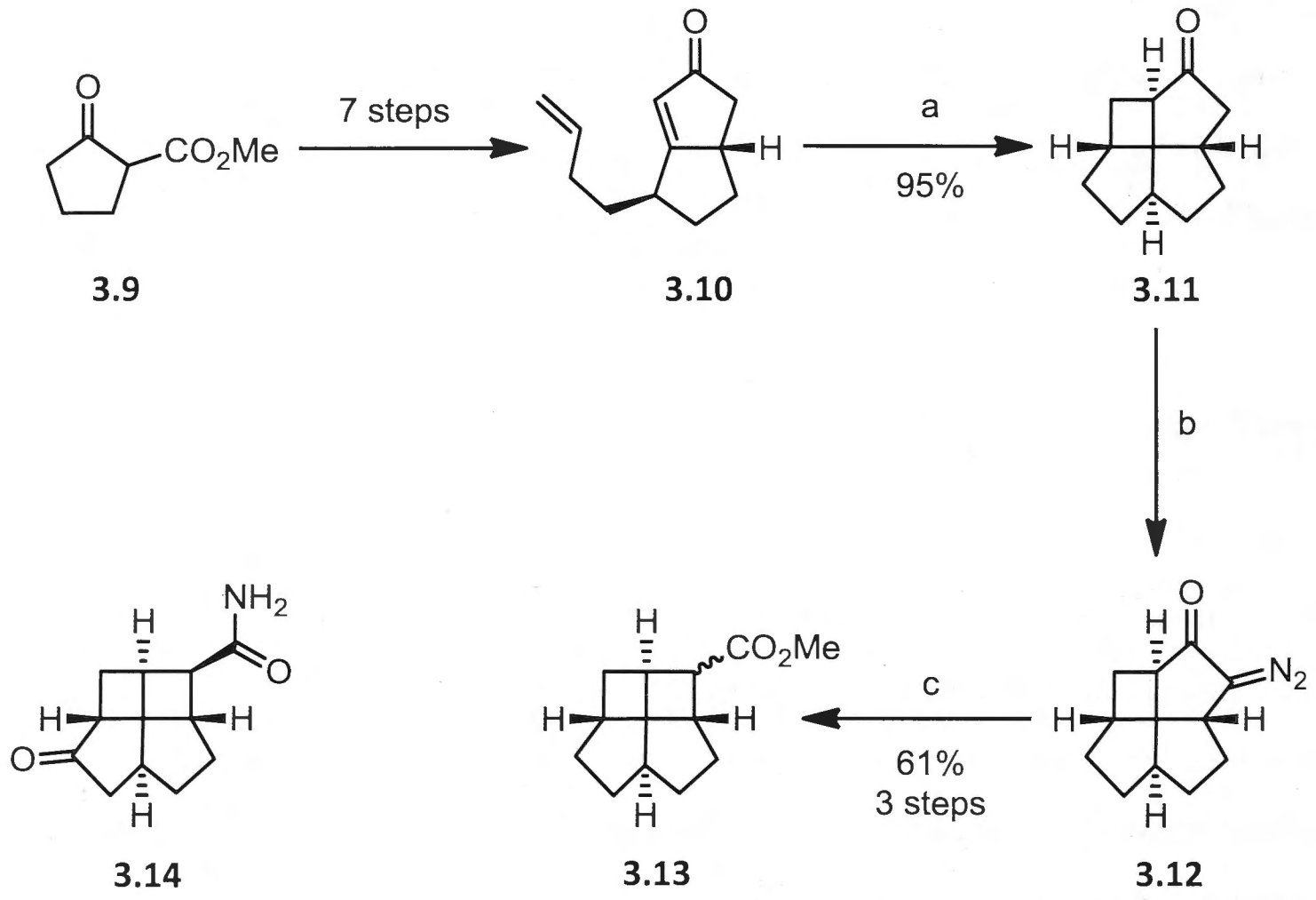


3.6 **3.7** **3.8**

Scheme 3.1. *Reagents and Conditions*: (a) i. pyrrolidine; ii. 3-buten-2-one; (b) hv, hexane.

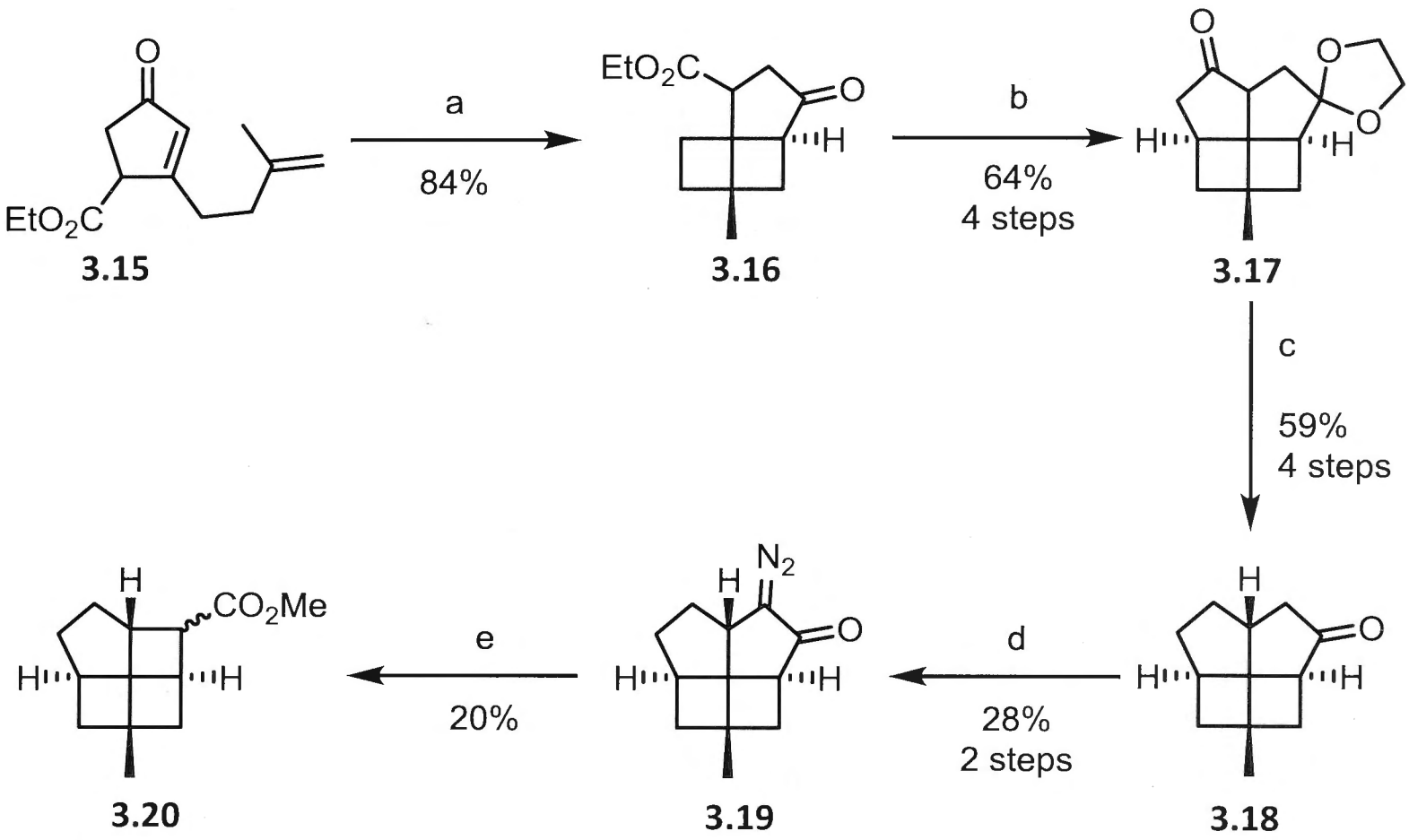
The forgoing approach was extended to the synthesis of various other fenestranes through the application of a Wolff rearrangement/ring-contraction reaction.[4b,5b,5c] Thus, Dauben and co-workers made [4.4.5.5]fenestrane[5b] **3.13** (Scheme 3.2) from the diquinane **3.10** that was itself synthesised from 2-carbomethoxycyclopentanone **3.9** in seven steps. Subjection of compound **3.10** to UV-irradiation effected an intramolecular [2+2]-cycloaddition reaction and so giving [4.5.5.5]fenestrane **3.11** in 95% yield. This last compound was itself committed to a deformylating diazo-transfer reaction so as to install a diazo-group next to the carbonyl moiety as seen in compound **3.12**. Irradiation of this last species with a 450 W lamp (to effect the Wolff-rearrangement) then gave [4.4.5.5]fenestrane **3.13** (the smallest fenestrane at the time) in 29% yield over eleven steps. Congener **3.14** was prepared in a similar way and could be

subjected to a single-crystal X-ray analysis which revealed a strong distortion of the geometry about the central carbon atom. Details are presented in Table 3.1.



Scheme 3.2. *Reagents and Conditions*: (a) hv (450 W, 330 nm), hexane, rt; (b) i. NaOH, ethyl formate, diethyl ether, 0 °C; ii. TsN_3, NEt_3, DCM, rt; (c) hv (450 W through Pyrex), MeOH, 0 °C.

Rao and co-workers[5c] used a generally similar approach but carried out the pivotal [2+2]-cycloaddition reaction on the monocyclic compound **3.15** (Scheme 3.3). This allowed for the simultaneous formation of two four-membered rings as embodied in the "broken" [4.4.5]fenestrane **3.16**. After protection of the associated ketone moiety the ester group within compound **3.16** was converted into the corresponding acid chloride which was itself treated with a solution of diazomethane to give the anticipated diazoketone. The rhodium-catalysed decomposition of this last species generated a carbenoid that engaged in a C-H insertion reaction onto the adjacent four-membered ring and thus affording [4.4.5.5]fenestrane **3.17**. Deletion of the associated carbonyl moiety and cleavage of the ketal gave compound **3.18** which, after functional group interconversions, yielded diazoketone **3.19**. Irradiation of this last compound at 310 nm then gave the desired [4.4.4.5]fenestrane **3.20** in 20% yield.[5c] The latter was converted into the crystalline *p*-bromoacetanilide derivative and this was subjected to a single-crystal X-ray analysis (see Table 3.1).[1b]



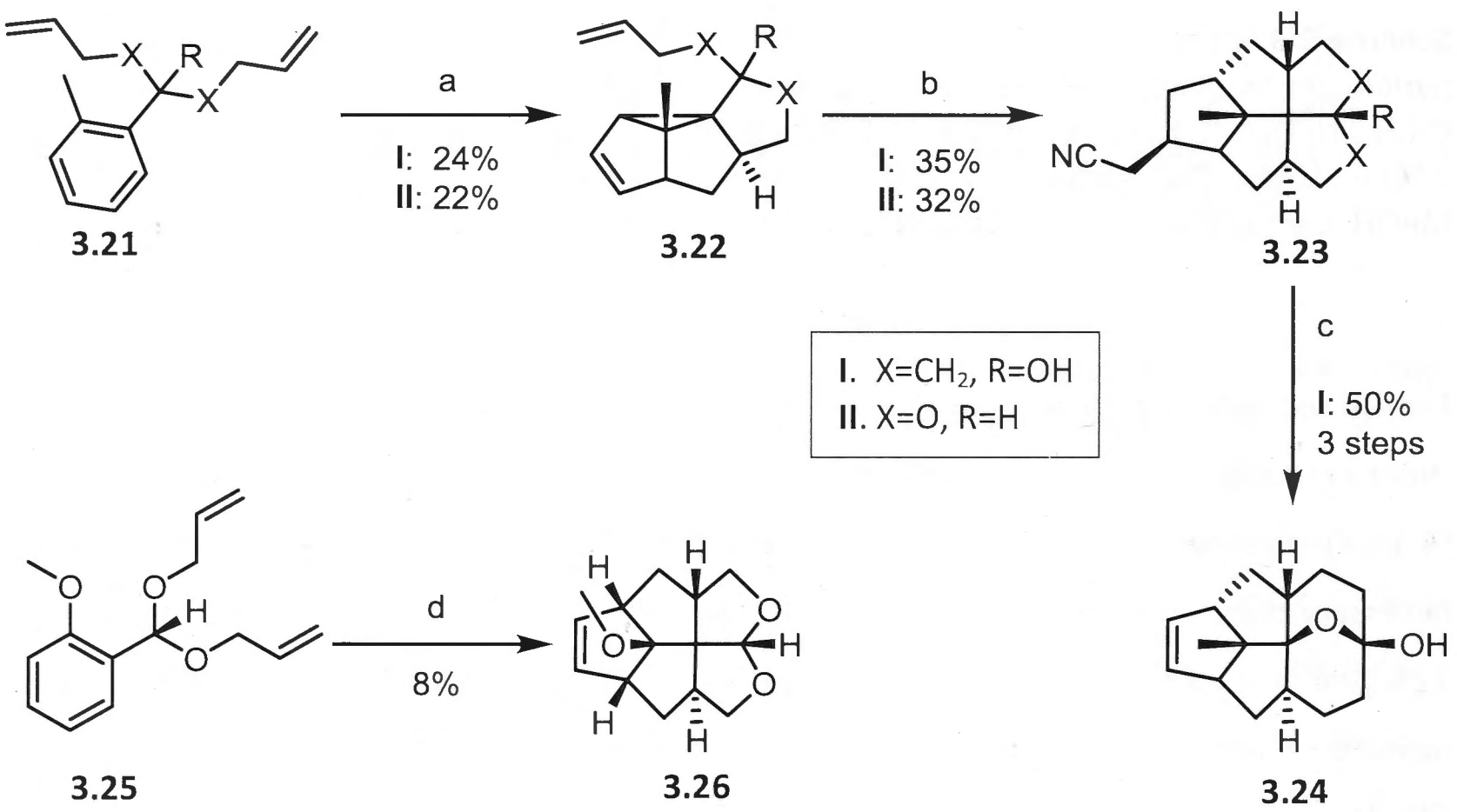
Scheme 3.3. *Reagents and Conditions*: (a) hv (450 W, 330 nm), hexane; (b) i. ethylene glycol, pyridinium tosylate, benzene, reflux; ii. KOH, 10% aq. MeOH, rt; iii. $(COCl)_2$, benzene then CH_2N_2, NEt_3, 0 °C to rt; iv. $Rh_2(OAc)_4$, DCM, rt; (c) i. $LiAlH_4$, diethyl ether, rt; ii. pyridine, *p*-TsCl, 0 °C; iii. $LiAlH_4$, THF, reflux; iv. *p*-TsOH·H_2O, 3% aq. acetone, rt; (d) i. NaH, ethyl formate, cat. MeOH, diethyl ether, 0 °C; ii. TsN_3, NEt_3, DCM, 0 °C; (e) hv (450 W through Pyrex), MeOH, rt.

Fenestrane **3.17** was functionalised in such a way that sequential ring-contractions using Wolff-rearrangement chemistry seemed possible and so suggesting a pathway to the unknown [4.4.4.4]fenestrane **3.1**. In the event, however, compound **3.17** proved a poor substrate for the necessary diazo-transfer reaction with the hoped-for derivative being obtained in less than 12% yield and with irradiation of it (to effect the Wolff-rearrangement) resulting in a complex mixture of products. As such this seemingly obvious approach to compound **3.1** must be considered ineffective.

Fenestranes Incorporating *trans*-Bicyclo[3.3.0]alkane Subunits

An entirely different approach to the construction of fenestranes was used by Wender *et al.* and this resulted in the incorporation of a *trans*-bicyclo[3.3.0]alkane subunit into [5.5.5.5]fenestranes[6a] of the general form **3.23** (Scheme 3.4). Thus, irradiation of compounds of the general form **3.21** at 254 nm induced a radical cascade reaction resulting in formation of cyclopropa-fused diquinanes of the general form **3.22**. Addition of the acetonitrile radical to the resulting cyclopentene ring was followed by trapping of the radical resulting from cyclopropane ring-cleavage by the tethered alkene and so producing fenestranes of the form **3.23**. Since the alkene side-chains within compounds **3.21** could be tethered to the aromatic

core using either an alkyl chain (**3.21-I**: X = CH_2) or an ether linkage (**3.21-II**: X = O) both all-carbon and heterocyclic fenestranes could be obtained using this strategy. The all-carbon [5.5.5.5]fenestrane **3.23-I** was manipulated so as to obtain a crystalline derivative suitable for single-crystal X-ray analysis. The derivative prepared for this purpose was the ring-expanded [5.5.6.6]fenestrane **3.24** and its analysis served to confirm the presence of the *trans*-bicyclo[3.3.0]alkane subunit. While the derivatisation method prevented comparison of the bond angles in the resulting product with those of other all-*cis* [5.5.5.5]fenestranes, by employing related *meta*-photocycloaddition protocols Penkett *et al.* were able to convert diene **3.25** into the *c,c,t,c*-oxa-[5.5.5.5]fenestrane **3.26**, the structure of which was confirmed directly by single-crystal X-ray analysis.[3]

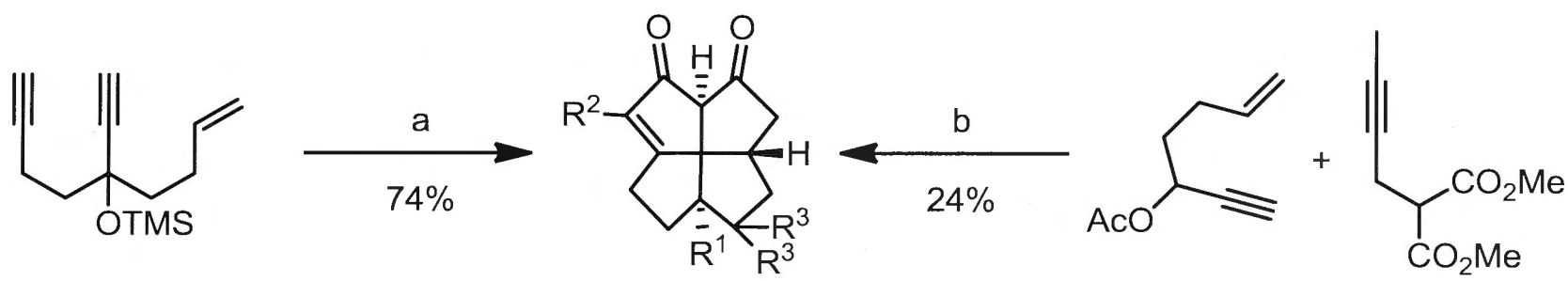


Scheme 3.4. *Reagents and Conditions*: (a) hv (254 nm, Vycor filter), cyclohexane; (b) $(PhCO_2)_2$, MeCN, 95 °C; (c) i. ^tBuOK, O_2, THF; ii. $Pb(OAc)_2$, $Cu(OAc)_2$; iii. NaOH, H_2O.

Fenestranes Embodying C-C Double Bonds at the Ring-Junction

Fenestranes incorporating ring junction double bonds can be formed by replacing the terminal alkene within compounds such as **3.10** (Scheme 3.2) with an alkyne and engaging the resulting substrates in analogous photochemically-promoted [2+2]-cycloaddition reactions. Another and particularly concise approach to these same systems employs Pauson-Khand chemistry. For example, a tandem Pauson-Khand reaction provided an efficient way of

assembling [5.5.5.5]fenestrane **3.28** in one step from diyne **3.27** (Scheme 3.5).[1c] Similarly, transition-metal catalysis in the presence of carbon monoxide allowed for the conversion of alkyne **3.29** into [5.5.5.5]fenestrane **3.31** in what constitutes a three-step/one-pot synthesis.[7]

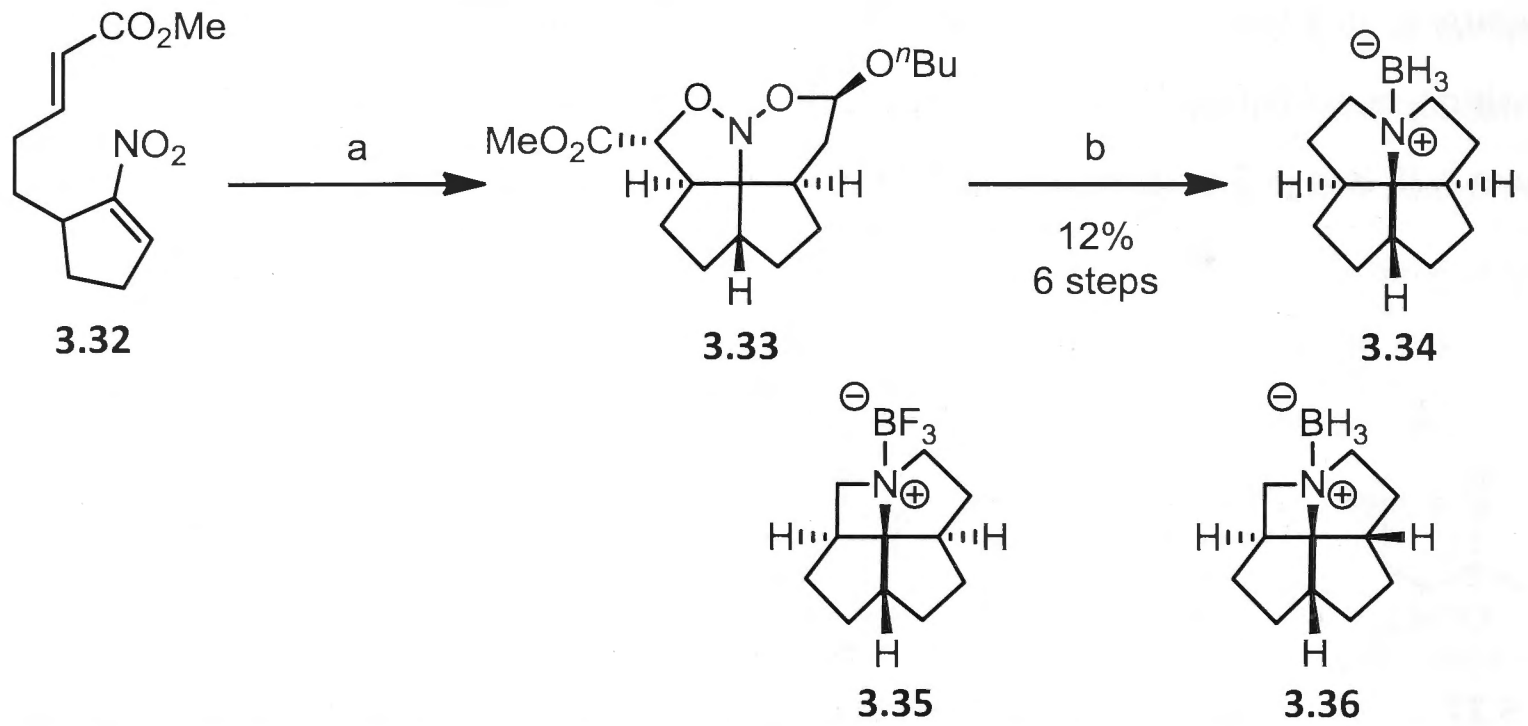


3.27 **3.28** R^1=OTMS, R^2=H, R^3=H; **3.31** R^1=H, R^2=Me, R^3=CO_2Me **3.29** **3.30**

Scheme 3.5. *Reagents and Conditions*: (a) i. $Co_2(CO)_8$; ii. NMO; (b) Co nanoparticles, CO (20 atm), THF, 130 °C then $[(n^3\text{-allyl})PdCl]_2$, dppe, **3.30**, BSA, KOAc, rt then CO (20 atm), 130 °C.

Heterocyclic Fenestranes

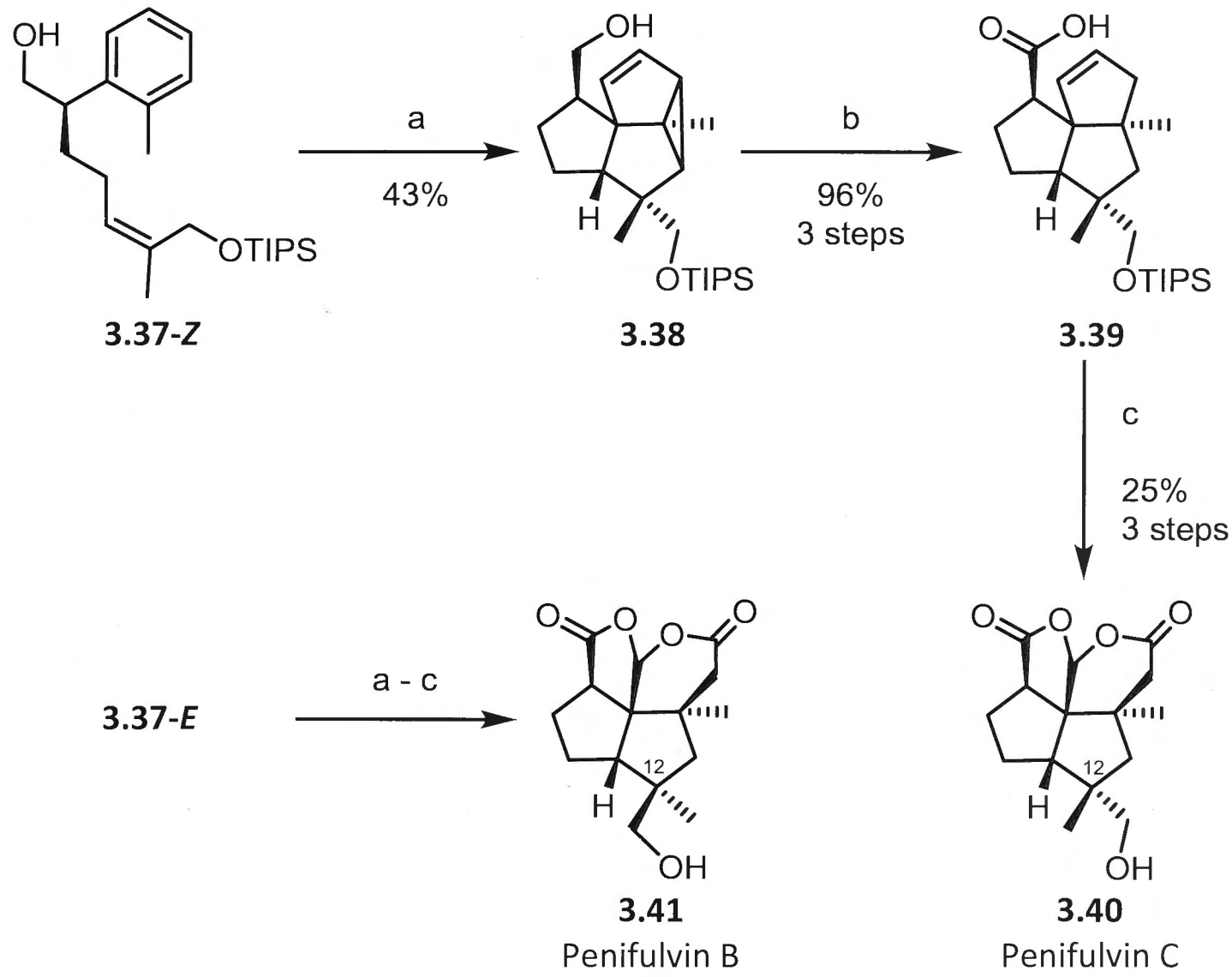
Various fenestranes incorporating oxygen atoms in place of the usual methylene units are known.[3,6,8] Furthermore, recent work by Denmark and co-workers has provided the first aza-fenestranes.[2] The motivation for incorporating nitrogen atoms was to facilitate the generation of crystalline fenestranes of various forms through formation of salts or BH_3-adducts. So, for example, nitroalkene **3.32** was treated with *n*-butyl vinyl ether in the presence of trimethylaluminium (Scheme 3.6) so as to induce an intramolecular [4+2]-cycloaddition reaction. The resulting nitronate underwent a spontaneous, intramolecular (3+2)-cycloaddition reaction yielding fenestrane **3.33**. Hydrogenation and functional group interconversions, followed by treatment with the BH_3·THF complex then gave the crystalline aza-[5.5.5.5]fenestrane **3.34**. The related all-*cis* aza-[4.5.5.5]fenestrane **3.35** and the *c,c,t,c*-aza-[4.5.5.5]fenestrane **3.36** were synthesised by analogous methods.



3.32 **3.33** **3.34** **3.35** **3.36**

Scheme 3.6. *Reagents and Conditions*: (a) i. *n*-Butyl vinyl ether, $AlMe_3$; (b) i. H_2, Raney-Nickel, MeOH; ii. *O*-Phenyl carbonochloridothioate, pyridine, DMAP; iii. AIBN, *n*-Bu_3SnH; iv. $LiAlH_4$, BH_3·THF.

A number of natural products embodying a fenestrane core have been reported and, in some cases, subjected to total synthesis studies. So, for example, elegant syntheses of two members of the penifulvin family – penifulvins B and C – were accomplished recently using Wender-type *meta*-photocycloaddition chemistry.[8-9] Thus, as shown in Scheme 3.7, the synthesis of penifulvin C (**3.40**), which only differs from penifulvin B (**3.41**) in the stereochemistry at C12, was prepared *via* irradiation of compound **3.37-*Z***, which resulted in the suprafacial (3+2)-cycloaddition of the *Z*-alkene onto the aromatic ring to give [5.5.5]fenestrane **3.38**. The *E*-isomer, **3.37-*E***, was used to establish an alternate stereochemical arrangement and so provide access to penifulvin B (**3.41**). Birch-type reduction conditions were used to cleave the associated cyclopropane and this was followed by oxidation of the hydroxymethyl group to give acid **3.39**. Ozonolysis of the associated C-C double bond resulted in formation of a hemiacetal that, upon subjection to oxidation and deprotection steps, gave the target compound penifulvin C (**3.40**).



Scheme 3.7. *Reagents and Conditions*: (a) hv (700 W Hg lamp, quartz filter), pentane, rt, 2 h; (b) i. Li, $EtNH_2$; ii. IBX, DMSO, rt; iii. $NaClO_2$, *t*-BuOH, NaH_2PO_4; (c) i. O_3, thiourea, DCM, −78 °C to rt; ii. cat AcOH, PDC, DCM; iii. 50% HF·pyridine, MeCN.

While the heteroatoms associated with these natural products are likely to have an influence on any planarising distortion about the central carbon, their precise effects have not been studied in any great detail, not least because no X-ray crystallographic data have been reported for penifulvins B and C.

3.1.3. Typical Geometries About the Central Carbon of Fenestranes

The semi-empirical calculations carried out by Keese and Thommen appear to predict the geometry about the central carbon of various fenestranes with reasonable accuracy.[1c] However, X-ray crystallography clearly provides the definitive means of determining the planarising effect of different ring sizes and/or the inclusion of *trans*-bicyclo[x.y.0]alkane subunits within the various possible fenestrane frameworks. Table 3.1 presents structural details arising from the single-crystal X-ray analysis of the small number of known and crystalline fenestranes. These are listed by ring-size and fall into three subclasses, namely the all-*cis* fused, the *trans*-fused bicyclo[x.y.0]alkane unit-containing, and the heteroatom-containing systems. The planarising distortion at the central carbon is defined (in the usual manner) by the two bond angles ρ and σ with the average of these two angles providing a

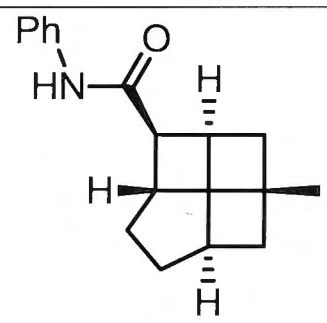
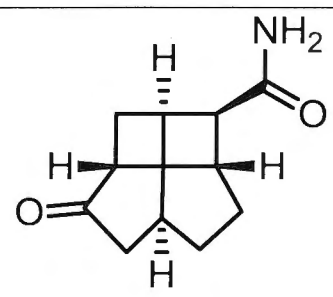
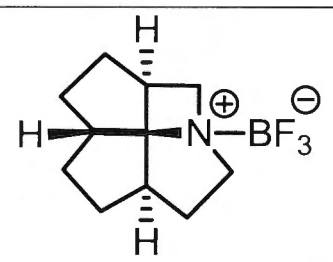
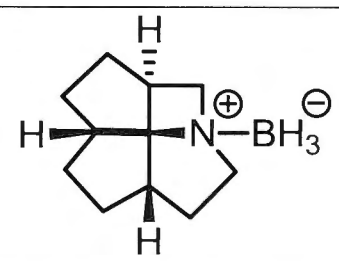
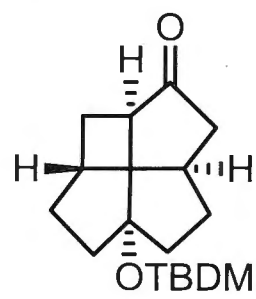
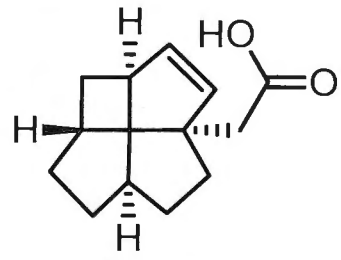
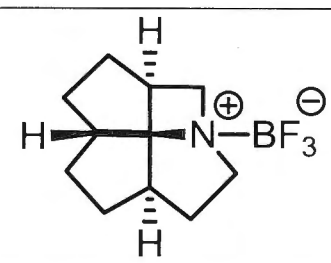
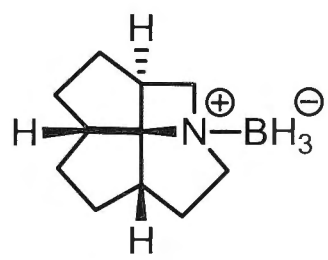
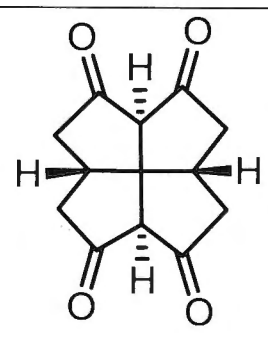
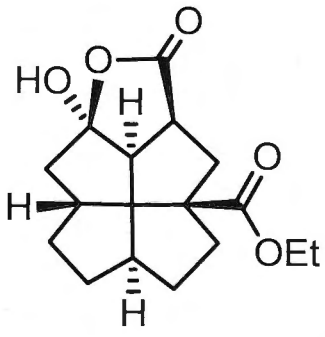
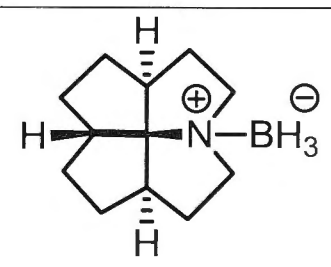
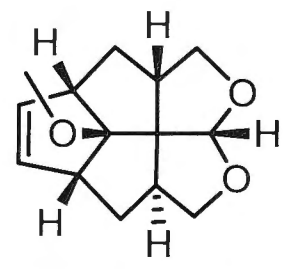
measure of the overall effect that any given structural feature has on the distortion of the geometry about the central quaternary carbon. In most publications the reported fenestrane bond angles were not explicitly assigned to either ρ or σ. Accordingly, and in order to facilitate discussion, it is assumed that the bond angles are given in the order ρ/σ (as was the convention introduced by Keese).

The first class of fenestranes, namely the [4.4.4.5]-system, consists of just one member: compound **3.42**. This was found to have bond angles of 129.2° (ρ) and 128.3° (σ) (average = 128.8) and represents the largest average deviation from normal tetrahedral geometry achieved to date within a fenestrane framework.[5c]

The second class also has just a single member, namely [4.4.5.5]fenestrane **3.14**. Here the relevant bond angles are 128.3° and 123.0° (average = 125.7) and so representing a system embodying more modest distortions to the geometry about the central carbon as compared with the lower homologue **3.42**. The precise origins of this change must be evaluated with care as compound **3.14** also features a ketone moiety that may well contribute to the observed bond angles.

The third class of fenestranes includes the *c,t,c,c*-[4.5.5.5]fenestranes **3.43** and **3.44** as well as the stereoisomeric aza-fenestranes **3.35** and **3.36**. Compounds **3.43** and **3.44** both incorporate a *trans*-fused bicyclo[x.y.0]alkane subunit, forcing the respective ρ-bond angles to 131.1° and 134°, while the (orthogonal) σ-bond angles are only moderately distorted (120.2° and 119°, respectively). Clearly, the *trans*-fusion of two of the associated rings causes a strong planarising distortion of one of the two angles. From this result it could be anticipated that inclusion of a second *trans*-arrangement of the constituent rings would cause a remarkable deviation from the tetrahedral bond angle for both ρ and σ. However, the average of the bond angles is 125.7° for compound **3.43** and 126.5° for compound **3.44**. The difference between the two ρ-bond angles of 131° and 134° may result from the position of the ring-junction substituent. While the relevant group within compound **3.43** is located on the *cis*-fused bicyclo[3.3.0]alkane subunit, the carboxylic acid residue within compound **3.44** is positioned on the *trans*-fused equivalent. Even though ring-junction substituents are predicted to have some impact on the planarising distortion[1c] no comprehensive study of this matter has been undertaken.

Table 3.1. Bond Angles (ρ/σ) of Various Types of Fenestranes.

Fenestrane Size	All-*cis*	*trans*-Fused Bicyclo-[x.y.0]-alkane Unit	Heterocycle
[4.4.4.5]	 **3.42**[1b]: 129.2°/128.3°		
[4.4.5.5]	 **3.14**[1b]: 128.3°/123.0°		
[4.5.5.5]	 **3.35**[2]: 121.3°/120.4°	 **3.36**[2]: 126.3°/120.7°  **3.43**[1f]: 131.1°/120.2°  **3.44**[1c]: 134°/119°	 *cis*-**3.35**[2]: 121.3°/120.4°  *trans*-**3.36**[2]: 126.3°/120.7°
[5.5.5.5]	 **3.45**[1b]: 117.5°/115.1°  **3.46**[1c]: 119.1°/117.3°		 **3.34**[2]: 116.6°/116.1°  *trans*-**3.26**[3]: 128.5°/120.2°

The precise effect of incorporating *trans*-bicyclo[3.3.0]alkane subunits becomes more apparent from a comparison of the stereoisomeric aza-[4.5.5.5]fenestranes **3.35** and **3.36**. Thus, while the all-*cis* fenestrane **3.35** has a ρ-bond angle of 121.3° (average = 120.9°), in its stereoisomer **3.36**, which incorporates one *trans*-ring fusion, a ρ-bond angle of 126.3° is observed. In contrast, the σ-bond angle only changes by 0.3°, resulting in an average of 123.5°.

Class four aza-[5.5.5.5]fenestrane **3.34** differs from congener **3.35** in that the four-membered ring is replaced by a five-membered one. The effect on the planarising distortion of the central carbon arising from this structural change is remarkable with a decrease of both bond angles, specifically by 4.7° for ρ and 4.3° for σ. This is the largest change in bond angles encountered thus far as a result of altering a single structural feature within a fenestrane subclass.

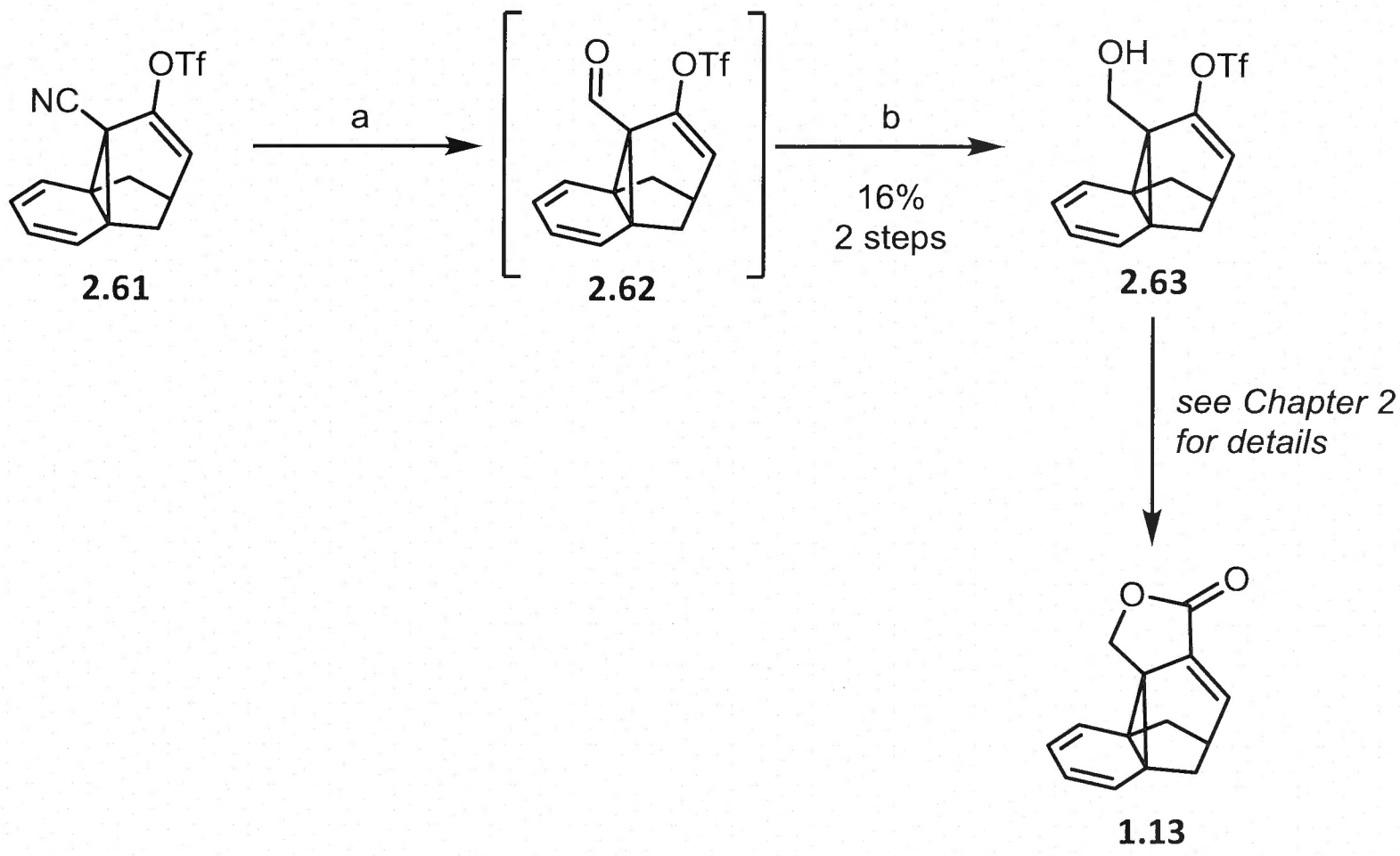
The all-*cis* [5.5.5.5]fenestranes **3.45** and **3.46** have similar bond angles, with those in the latter being an average of almost 2° higher. This is most likely due to compound **3.46** being conformationally restricted by the bridging lactone. However, the possibility that the ring-junction substituent influences this difference cannot be discounted.

The influence of heteroatoms on the planarising distortion doesn't appear to be significant. Thus, for example, a comparison of the [5.5.5.5]fenestranes **3.45** and **3.34** shows that the relevant bond angles are very similar. Unfortunately, the absence of X-ray data on systems incorporating additional structural features such as differing substituents has prevented a rigorous assessment of the impact of such features.

The above-mentioned results confirm theoretical predictions[1c] that the planarising distortion of the geometry about the central fenestrane carbon is influenced by ring-size, the presence of *trans*-fused rings and ring-junction substituents. According to the data obtained through X-ray analysis, the largest influence on planarising distortion arises from the inclusion of four-membered rings, as emphasised by comparing aza-fenestranes **3.35** and **3.34** where there is an average change in bond angles of 4.5°. The impact of the inclusion of *trans*-bicyclo[x.y.0]alkane subunits, as seen from the comparison of aza-fenestranes **3.35** and **3.36** (average change in bond angles of 2.6°), can also be significant. Ring-junction substituents seem to have a relatively minor effect on the bond-angles while the incorporation of heteroatoms has hardly any impact at all.

3.2. The DIBAL-H Reduction of Nitrile 2.61

As noted in the preceding Chapter, part of the efforts directed towards the total synthesis of salvileucalin B (**1.3**) involved reduction of the nitrile function within propelladiene **2.61** so as to give alcohol **2.63** (Scheme 3.8) which was then converted into lactone **1.13**, a compound embodying the caged core of the target natural product.



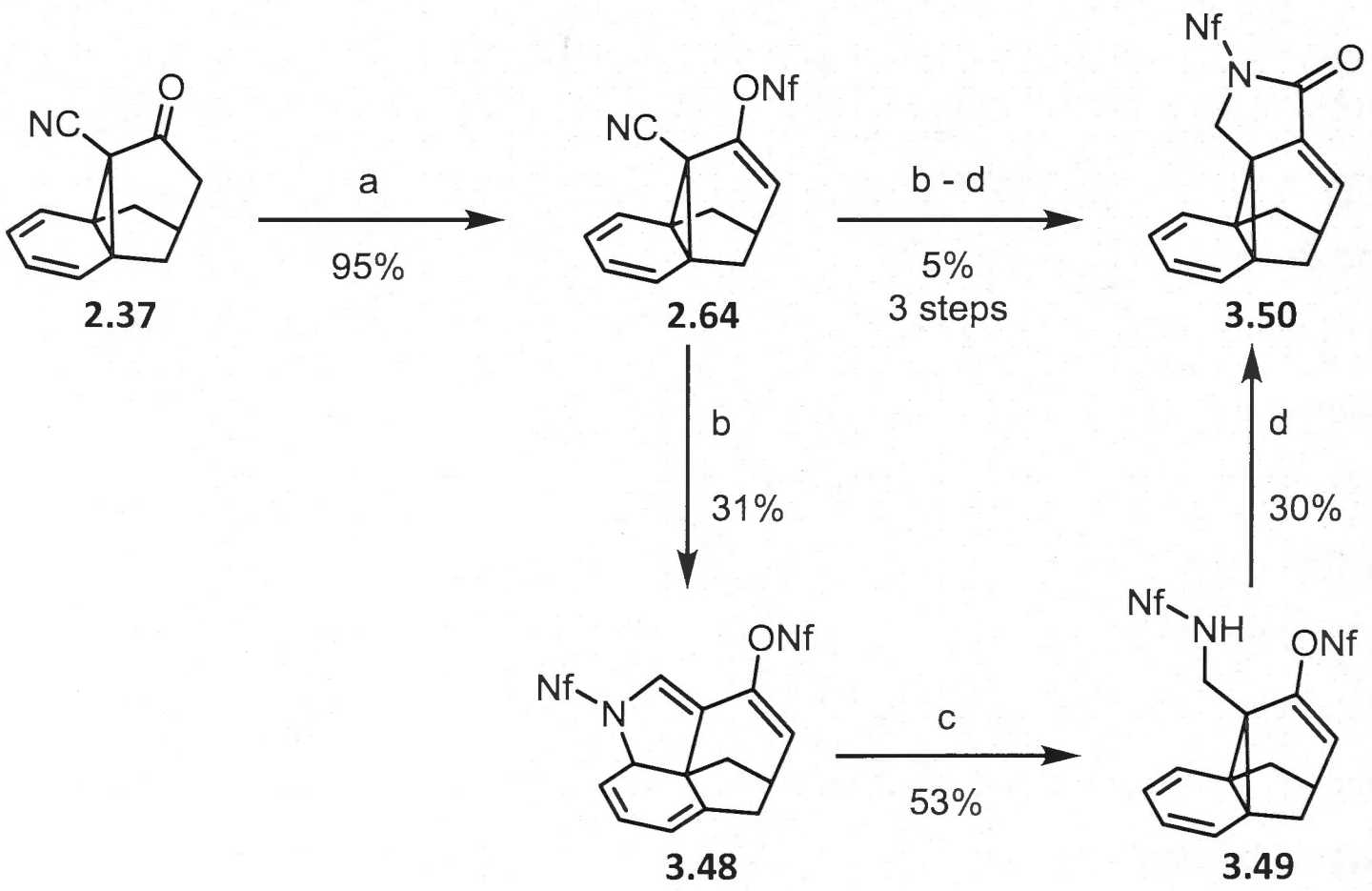
2.61 **2.62** **2.63** **1.13**

Scheme 3.8. *Reagents and Conditions*: (a) DIBAL-H, DCM, −40 °C; (b) DIBAL-H, DCM, −78 °C.

The DIBAL-H-mediated conversion **2.61** → **2.63** turned out to be a rather complex reaction.[10] Not only was it a low-yielding process, it was also very sensitive to reagent quality and the method used for the work up. The primary product obtained from DIBAL-H reduction of the nitrile function within compound **2.61** appeared to be very unstable and even when maintained under nitrogen atmosphere it discoloured very rapidly. As such it was immediately subjected to a second DIBAL-H-mediated reduction after rudimentary purification and thus providing the desired alcohol **2.63** albeit in rather poor yield. Efforts to establish a one-pot reaction sequence for the conversion **2.61** → **2.63** were unsuccessful as the quenching of the reaction mixture obtained after the first DIBAL-H reduction step needed to be thorough (*i.e.* addition of an excess of aqueous quenching solution was required) in order for the final product to be obtained (*vide infra*). Similar observations have been made by the Reisman group.[11]

3.2.1. Using the Enol Nonaflate 2.64 as the Substrate in the DIBAL-H Reduction Step

The low yields associated with the DIBAL-H reduction of compound **2.61** could be attributed, in part at least, to the sensitivity of the associated enol triflate moiety. As such it was envisaged that a nonaflate group would offer greater stability and thus increase the yield of the required primary alcohol. Accordingly, enol nonaflate **2.64** was generated from β-keto nitrile **2.37** using LiHMDS and perfluoro-1-butane sulfonyl fluoride in THF at 0 °C (Scheme 3.9). When the resulting compound **2.64** was subjected to DIBAL-H-mediated reduction using the previously employed conditions then a crystalline compound was isolated although this was prone to decomposition upon standing. The ^{1}H NMR spectrum of this product was remarkably similar to that of the compound obtained from reduction of the original triflate **2.61**, and so it was carried through the same reaction sequence as used for the synthesis of core lactone **1.13** (*viz.* **3.48** → **3.49** → **3.50**) as described in Chapter 2. The ^{1}H NMR spectrum of the material obtained at the end of this sequence indicated that, once again, a symmetrical diene had been obtained. Eventually, the product of the initial DIBAL-H-mediated reduction was subjected to single-crystal X-ray analysis and this revealed that it was the nitrogen-containing fenestrane **3.48** (Scheme 3.9). On this basis, it was ultimately concluded that the compound resulting from its further elaboration (using DIBAL-H) was the nonaflate-protected lactam **3.50**, the mass spectrum of which displayed a base peak at *m/z* 210 that corresponds to the loss of the nonaflate group from the molecular ion (which was not observed).

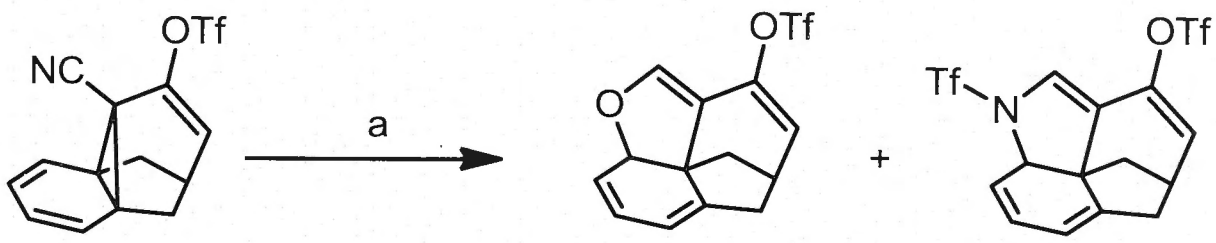


Scheme 3.9. *Reagents and Conditions*: (a) LiHMDS, perfluoro-1-butanesulfonyl fluoride, THF, 0 °C; (b) DIBAL-H, DCM, −78 C; (c) $NaBH_4$, EtOH, 0 °C; (d) CO (1 atm), $Pd(PPh_3)_4$, LiCl, NEt_3, THF, rt.

Attempts to alter the quenching process associated with the second step shown in Scheme 3.9 in order to generate the oxygen-containing heterocyclic counterpart to compound **3.48** were unsuccessful. This unexpected reactivity was attributed to the hydrophobic nature of the nonafluoro chain. So, during the reduction process, a nonaflate group (presumably originating from another molecule of nitrile **2.64**) migrated to the negatively charged nitrogen arising from reduction of the nitrile. Once this migration had occurred (and so forming a *bis*-nonaflate-containing system) the compound was too hydrophobic to engage in any reaction with water. As a result a sigmatropic rearrangement (see Scheme 3.11 for the analogous process involving the triflate-containing system) then occurred, resulting in the formation of the observed aza-fenestrane **3.48**, a process that can only deliver this compound in a maximum of 50% yield (based on the starting nitrile **2.64**). The byproduct that was expected to arise from loss of the nonaflate group within nitrile **2.64** was not found in the reaction mixture. The best recorded yield for this reaction was 31% (or 62% based on the theoretically possible yield of the product).

3.2.2. Oxa- and Aza-Fenestranes

Since the use of the nonaflate group in the above-mentioned sequence did not offer any advantages, the research focus returned to enol triflate **2.61** as the substrate for the pivotal DIBAL-H-mediated reduction. Upon closer inspection of the complex reaction mixture obtained from this process, it was found that the triflate-containing aza-fenestrane **3.52** had been formed and its structure was confirmed by single-crystal X-ray analysis (details of which are provided in Appendix 5). Based on these results and the unusual chemical shifts observed in the ^{1}H NMR spectrum of the co-produced oxygen-containing compound it was concluded that this was most likely the oxa-[5.6.5.6]fenestrane **3.51** (Scheme 3.10).



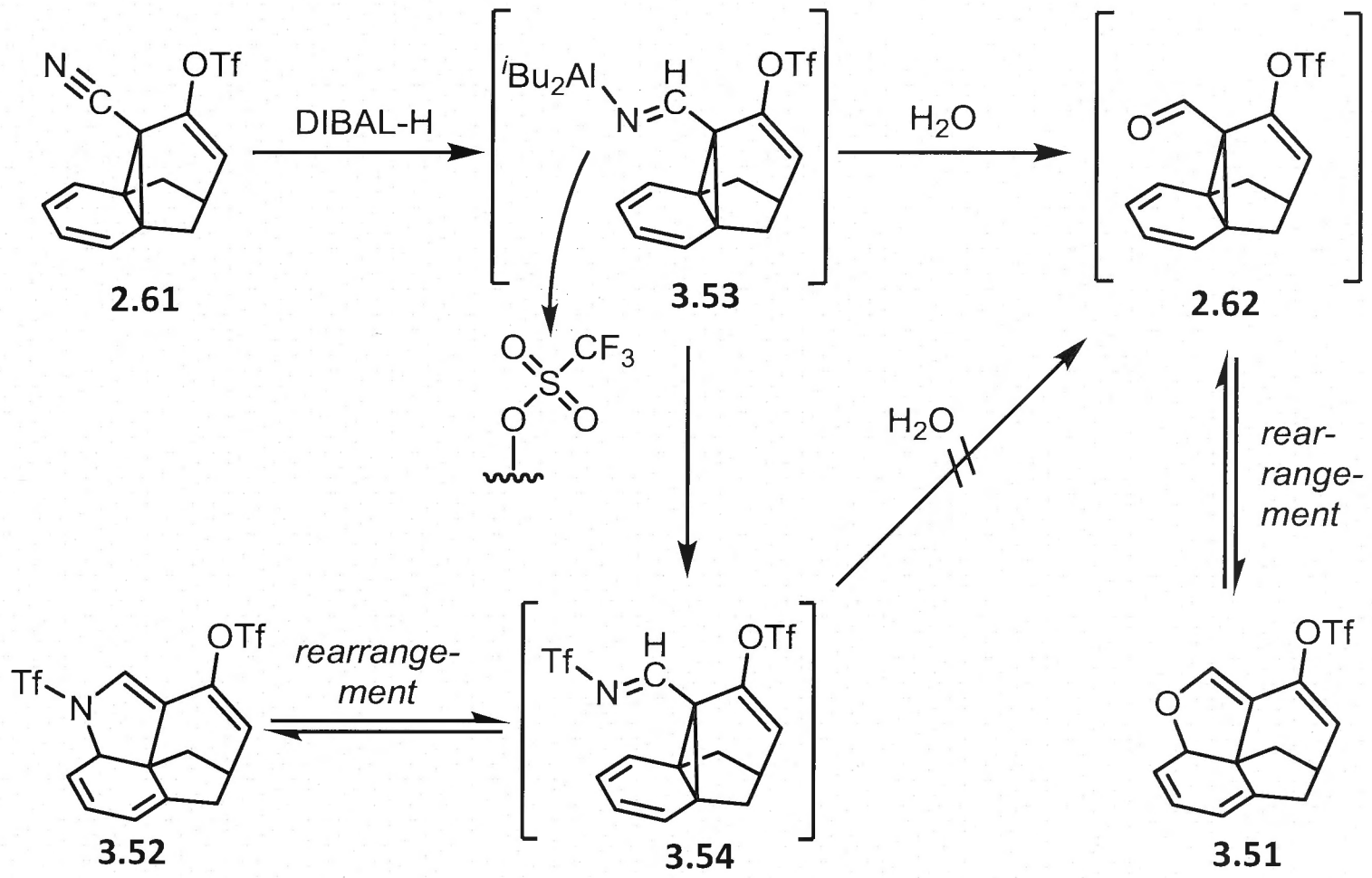
2.61	*Workup:*	**3.51**	**3.52**
	Rochelle salt method	10%	15%
	HCl-method	49%	-

Scheme 3.10. *Reagents and Conditions*: (a) DIBAL-H, DCM, −40 °C.

As a result of this discovery, further screening of work up methods associated with the reduction process was undertaken and such that it was eventually found that addition of 1 M aq. HCl to the quenched reaction mixture, followed by vigorous stirring until both layers of the two-phase mixture were clear, gave better yields of oxa-fenestrane **3.51**. Interestingly, while an HCl-based quenching step resulted in formation of oxa-fenestrane **3.51**, a Rochelle salt-based quenching step favoured the formation of the aza-fenestrane **3.52**. In only a very few cases was oxa-fenestrane **3.51** isolated as the sole product of the reaction. Another major factor influencing the product distribution in this process turned out to be the quality of the DIBAL-H solution used. The best results, *i.e.* those delivering the highest yield of oxa-fenestrane **3.51**, were obtained when using a new bottle of DIBAL-H (used as a 1 M solution in hexane). Older batches of this reagent, even those still delivering high yields in other (simple) carbonyl reductions, gave poor yields of oxa-fenestrane **3.51**. Under such circumstances the amounts of aza-fenestrane **3.52** and recovered starting material increased.

3.2.3. The Effect of DIBAL-H Quality on Product Distribution

The precise origins of the impact of the workup method on product distribution are still not entirely clear. However, the influence of DIBAL-H quality could be explained by the mechanism presented in Scheme 3.11. Thus, the Lewis-acidic aluminium of the DIBAL-H coordinates to the nitrogen of the nitrile and thereby delivers hydride to the nitrile group carbon. There are two possible pathways by which the intermediate **3.53** so formed can be carried forward. Either, this compound could be trapped by a triflate group of another molecule and thereby forming compound **3.54**, or it could be hydrolysed by the added saturated aqueous solution of Rochelle salt or the added dilute acid and so forming the desired aldehyde **2.62**. Products **3.54** and **2.62** would then rearrange to give the corresponding aza-fenestrane **3.52** or oxa-fenestrane **3.51**, respectively. Such arguments suggest that once formed, bis-triflate **3.54** does not hydrolyse to the corresponding aldehyde. For its nonaflate-containing counterpart **3.48** this lack of hydrolysis can be attributed to its hydrophobic character. In the case of the triflate-containing compound **3.54** it is also possible to attribute this lack of hydrolysis to the stabilising effect the triflate group exerts on the nitrogen.



Scheme 3.11. Proposed pathways for the quenching of aluminium-complexed species **3.53** and the associated formation of fenestranes **3.51** and **3.52**.

3.2.4. Proving the Structure of Oxa-Fenestrane 3.51

The first clear indication that oxa-fenestrane **3.51** was the primary product of DIBAL-H reduction of nitrile **2.61**, and not the originally anticipated aldehyde **2.62**, was the absence of any resonances due to aldehydic protons in the ^{1}H NMR spectrum (Figure 3.2). Rather, a one-proton singlet was observed at δ 6.51 together with five resonances due to hydrogens attached to sp^2-hybridised carbons. One of these, the doublet at δ 5.78, was assigned to the hydrogen of the enol triflate moiety.

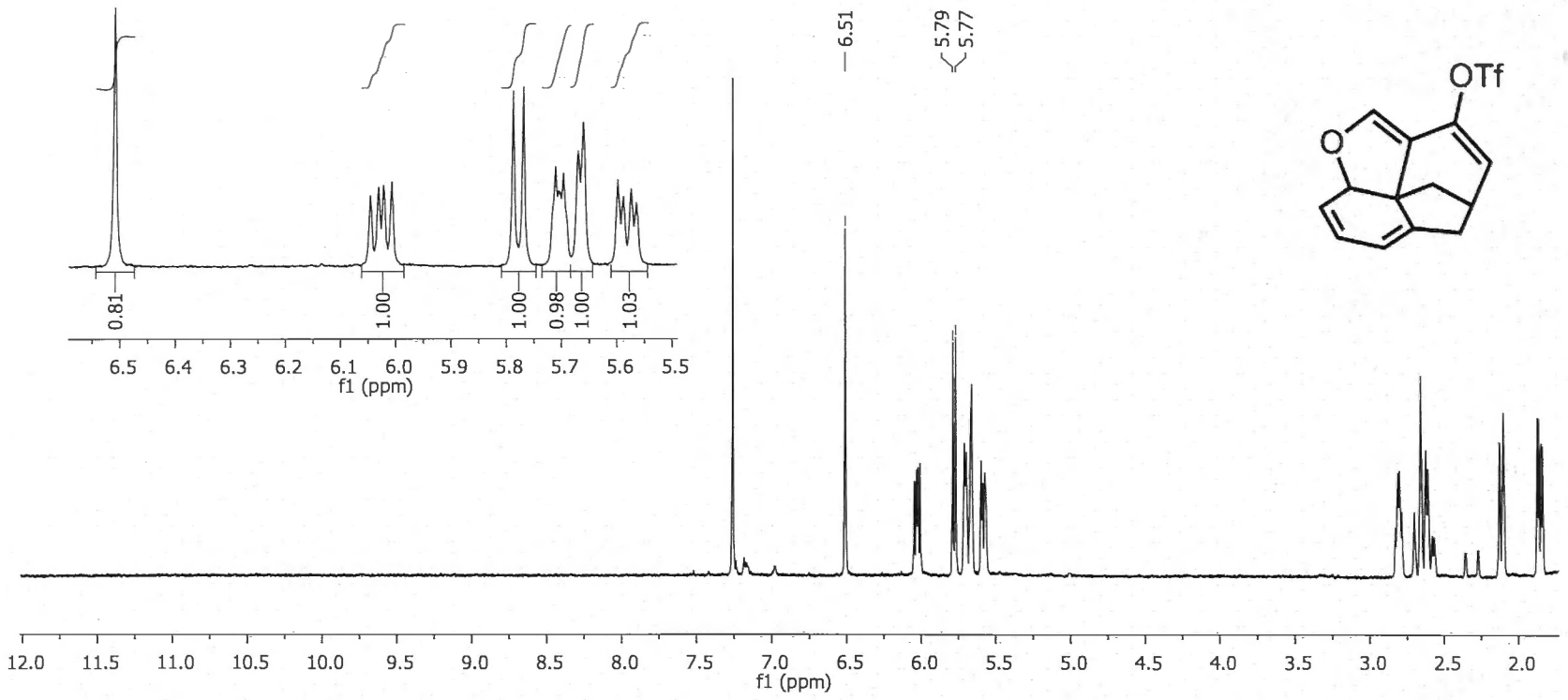


Figure 3.2. 300 MHz ^{1}H NMR spectrum of oxa-fenestrane **3.51** (recorded in $CDCl_3$).

As discussed above, co-produced triflimide **3.52** was isolated from the DIBAL-H reduction and its [5.6.5.6]fenestrane structure confirmed by single-crystal X-ray analysis. Its ^{1}H NMR spectrum (Figure 3.3) was very similar to that of the oxa-fenestrane (**3.51**) and on the basis of such comparisons it was concluded that the oxa-analogue **3.51** had been obtained rather than the isomeric aldehyde **2.62**.

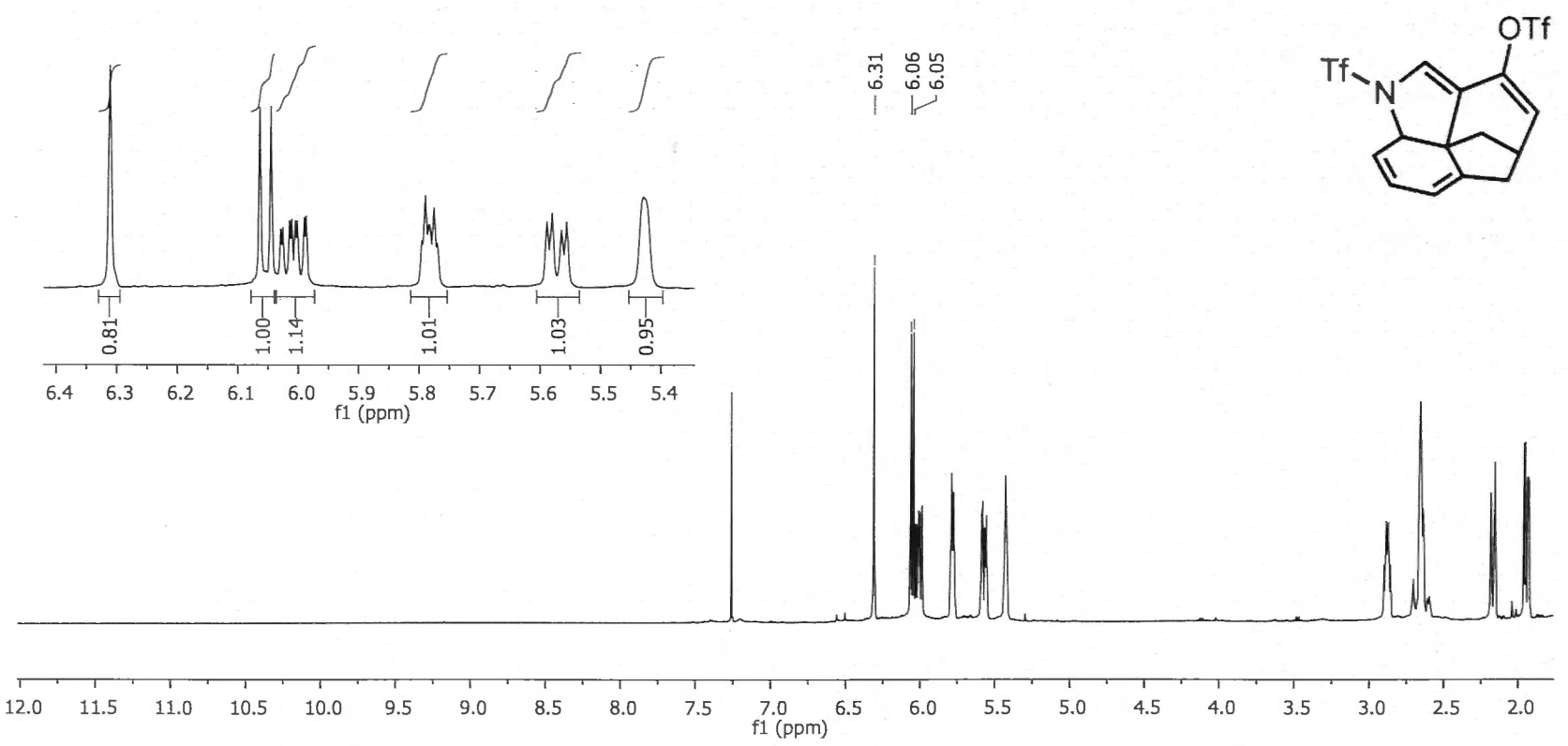


Figure 3.3. 300 MHz ^{1}H NMR spectrum of aza-fenestrane **3.52** (recorded in $CDCl_3$).

The most straightforward way of confirming the structure of the rearrangement product **3.51** was by two-dimensional H,H- and C,H-correlation NMR spectroscopy. In particular, the COSY spectrum of this compound clearly showed the four downfield resonances due to the methine protons of the cyclohexadiene substructure (Figure 3.4). These appeared as two doublets of

doublets and two doublets. The HSQC spectrum also showed a correlation between one of the two 'terminal' (at one end of the diene substructure) hydrogens and a signal at δ_C 84.0 in the ^{13}C NMR spectrum (Figure 3.5). This chemical shift is characteristic of an aliphatic carbon adjacent to the oxygen within alkyl vinyl ether moieties[12] and thus suggesting that it was due to C11. Interestingly, the signal due to the equivalent carbon in the aza-fenestrane **3.52** appeared at δ_C 66.0. All of these data clearly indicate that the primary product of the DIBAL-H reduction process is the fenestrane **3.51** and not the isomeric system **3.55** that the arguments presented by Reisman[11] would suggest to be the case.

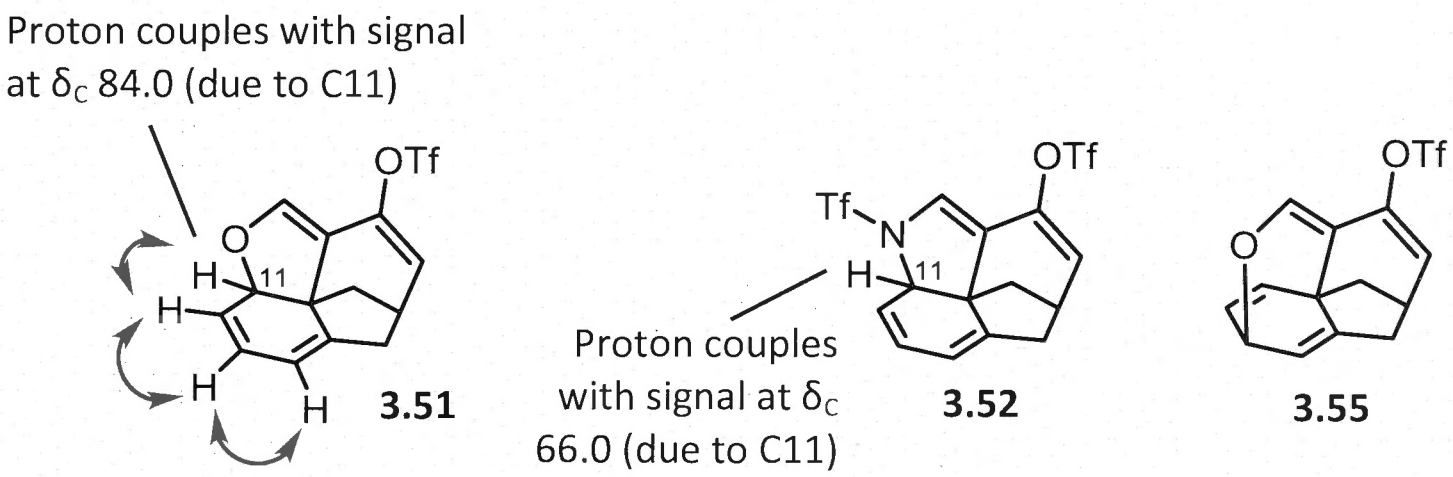


Figure 3.4. Key NMR spectroscopic evidence for the structures of fenestranes **3.51** and **3.52**. The blue arrows indicate the H,H-correlation observed in the COSY spectrum.

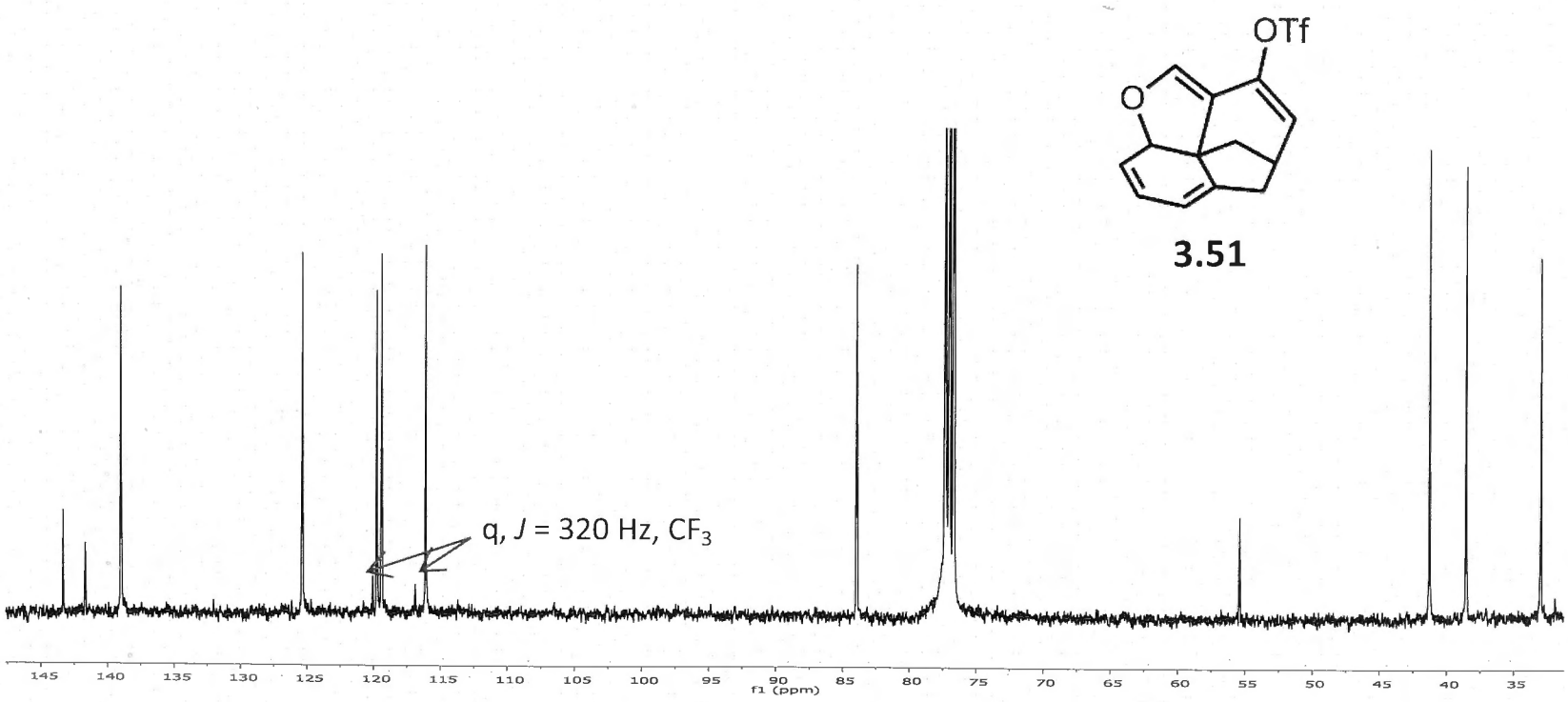
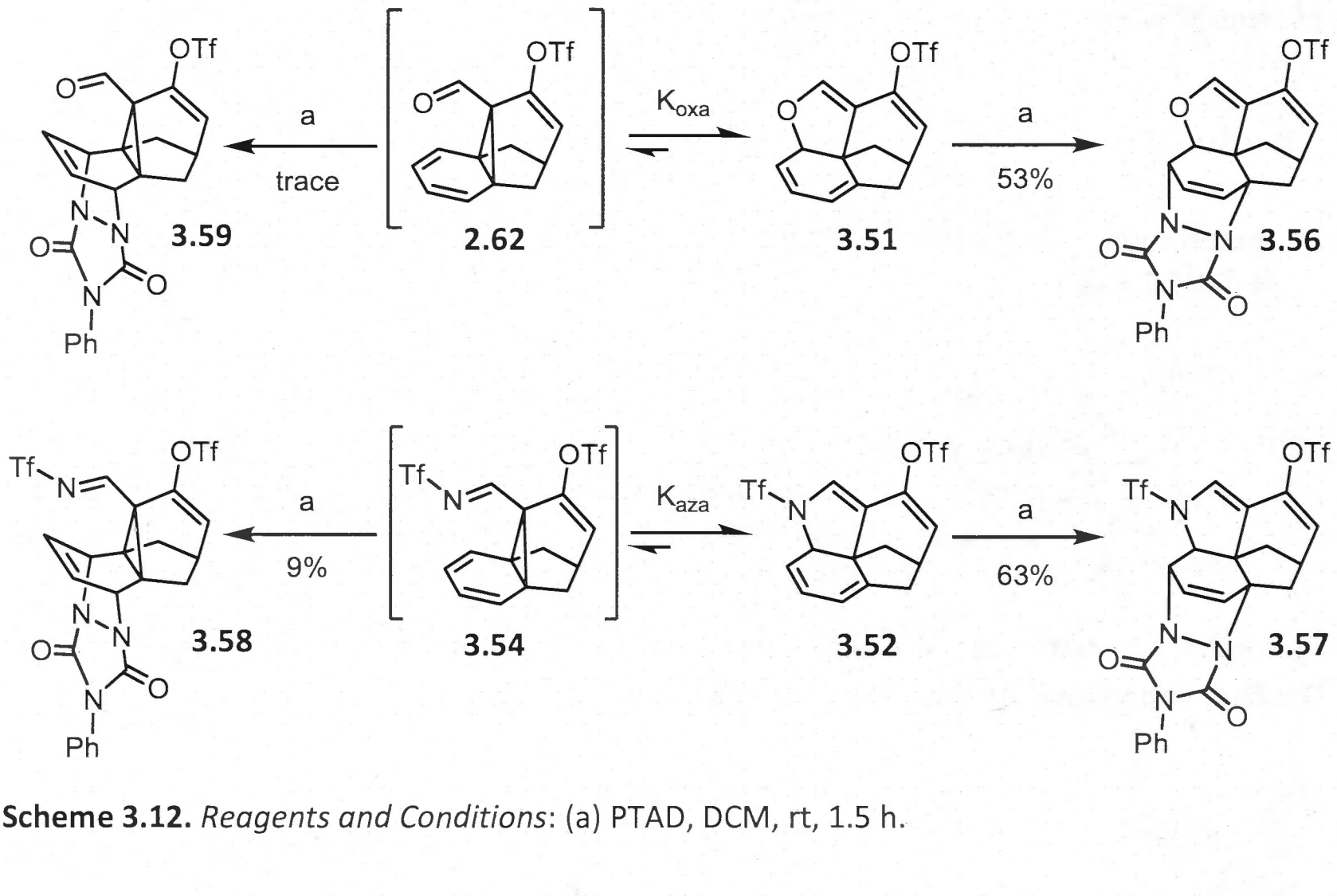


Figure 3.5. 75 MHz ^{13}C NMR spectrum of oxa-fenestrane **3.51** (recorded in $CDCl_3$).

In order to secure further information about compound **3.51**, most particularly its mode of formation and the manner in which it reacts, it was treated with PTAD in DCM at room temperature (Scheme 3.12). The only product isolated from this reaction was the crystalline Diels-Alder adduct **3.56** (53%) and the structure of which was confirmed by single-crystal X-ray

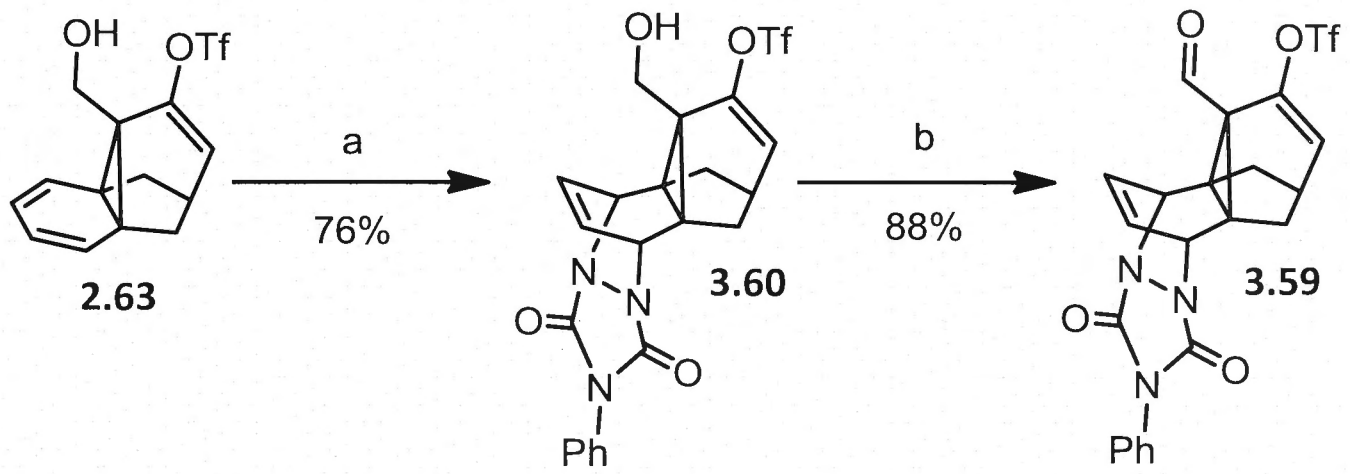
analysis (see Appendix 6). The cycloaddition process leading to this compound had clearly taken place at the less sterically hindered face of the s-*cissoid* diene moiety within substrate **3.51**, resulting in formation of a *trans*-fused bicyclo[4.3.0]alkane subunit. The relatively low yield of this reaction is attributed to the unstable nature of oxa-fenestrane **3.51** which is observed to slowly decompose on standing at room temperature.



Scheme 3.12. *Reagents and Conditions*: (a) PTAD, DCM, rt, 1.5 h.

When aza-fenestrane **3.52** was exposed to the same dienophile, it displayed a similar reactivity and formed the analogous PTAD-adduct **3.57**, although this could not be obtained in crystalline form. A second adduct, the symmetrical propellane **3.58**, was obtained in 9% yield and this presumably arises from a [4+2]-cycloaddition reaction between the norcaradiene **3.54** and PTAD. This outcome suggests that compounds **3.52** and **3.54** are in equilibrium with one another with the latter predominating to a significant extent. These results imply that the equilibrium constant for the rearrangement of the aza-fenestrane (*viz.* **3.54** → **3.52**), K_{aza}, is smaller than that for the oxa-analogue (*viz.* **2.62** → **3.51**), K_{oxa}, which did not form any equivalent symmetrical PTAD-adduct. Thus, the imine-propellane valence bond isomer **3.54** has a slightly increased concentration in the propellane-fenestrane equilibrium. This difference in equilibrium constants is probably due to a stabilising effect exerted by the triflate group on the nitrogen atom, the same effect responsible for the lack of hydrolysis of compound **3.54** to form the corresponding aldehyde **2.62** (see Scheme 3.11).

When PTAD was added to the crude product obtained from the initial DIBAL-H reduction, a trace of adduct **3.59** arising from a Diels-Alder reaction between the dienophile PTAD and aldehyde **2.62** was observed. The identity of this product was proven through its independent synthesis by oxidation of the PTAD adduct of alcohol **2.63** as shown in Scheme 3.13. Such observations provided further proof of the interconversion of aldehyde **2.62** and its ring-opened valence-tautomer (*viz.* fenestrane **3.51**) and between triflimide **3.54** and the corresponding aza-fenestrane **3.52**.

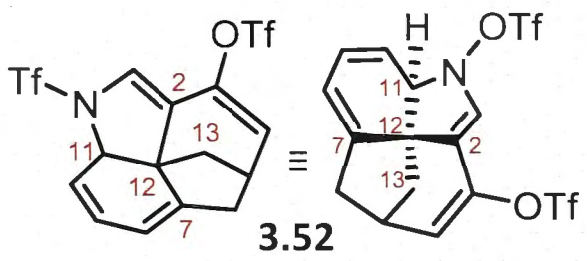
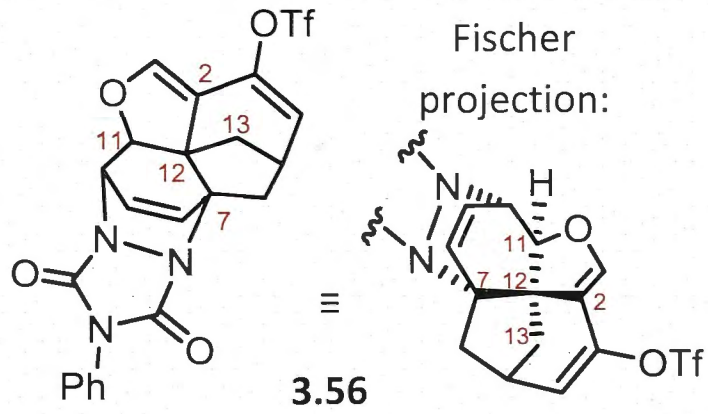


Scheme 3.13. *Reagents and Conditions*: (a) PTAD, DCM, rt, 1 h; (b) PCC, silica gel, DCM, rt, 1 h.

3.2.5. Key Structural Features Associated with the Fenestranes 3.52 and 3.56

While Keese and Thommen have suggested that the orthogonal bond angles ρ and σ provide an important indicator of the planarising distortion of the central carbon of the fenestranes,[1c] it is also interesting to consider the remaining bond angles within such systems. These can be compressed to values well below the tetrahedral angle of 109.5°. As noted earlier, the crystalline [5.6.5.6]fenestranes **3.52** and **3.56** described above were subjected to single-crystal X-ray analysis in order to determine the planarising distortion around the central carbon atom and the key angles determined by such means are presented in Table 3.2.

Table 3.2. Key Bond Angles Associated with the Solid State Structures of Aza-Fenestrane **3.52** and Oxa-Fenestrane Derivative **3.56**.

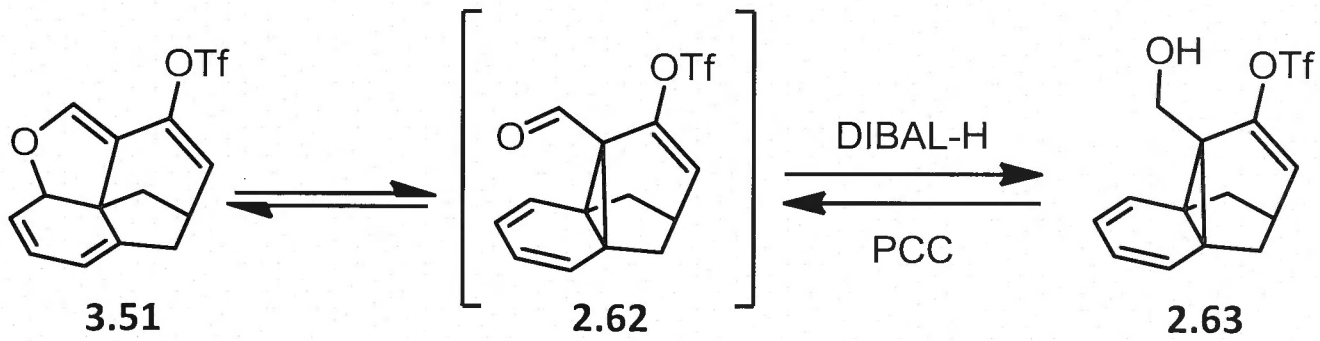
Atom array	Fischer projection:  **3.52**	 **3.56**
ρ: C11-C12-C13	121.2°	126.0°
σ: C2-C12-C7	112.7°	113.5°
C2-C12-C11	102.6°	101.0°
C7-C12-C11	115.1°	109.4°
C7-C12-C13	100.5°	100.1°

Thus, aza-fenestrane **3.52** displays ρ- and σ-bond angles of 121.2° and 112.7°, which are quite distorted for a [5.6.5.6]fenestrane. By comparison, the previously reported and smaller all-*cis* [5.5.5.5]fenestrane **3.45** (Table 3.1) has ρ- and σ-bond angles of 117.5° and 115.1°. Accordingly, the distortion observed for the aza-fenestrane **3.52** must be attributed to the presence of the diene moiety. Indeed, the central bond angle most affected by the geometry of sp^2-hybridised carbons (C7-C12-C11) is stretched to 115.1°. For both fenestranes **3.52** and **3.56** the central angles incorporated in the five-membered heterocycle are 102.6° and 101.0°, respectively, which can be taken as indicators of high degrees of compression. The same can be said for the opposite five-membered ring where values of 100.5° and 100.1° are observed.

Interestingly, the ρ- and σ-bond angles of PTAD-adduct **3.56** were only 126.0° and 113.5°, respectively, which is rather low for a fenestrane including a *trans*-fused subunit. However, this situation can be attributed to the larger ring sizes associated with this [5.6.5.6]fenestrane, a feature which reduces the effect of such *trans*-fused subunits.

3.3. Deducing the Mechanism of the Formation of Fenestratetraenes 3.51 and 3.52 from Propelladienes 2.62 and 3.54

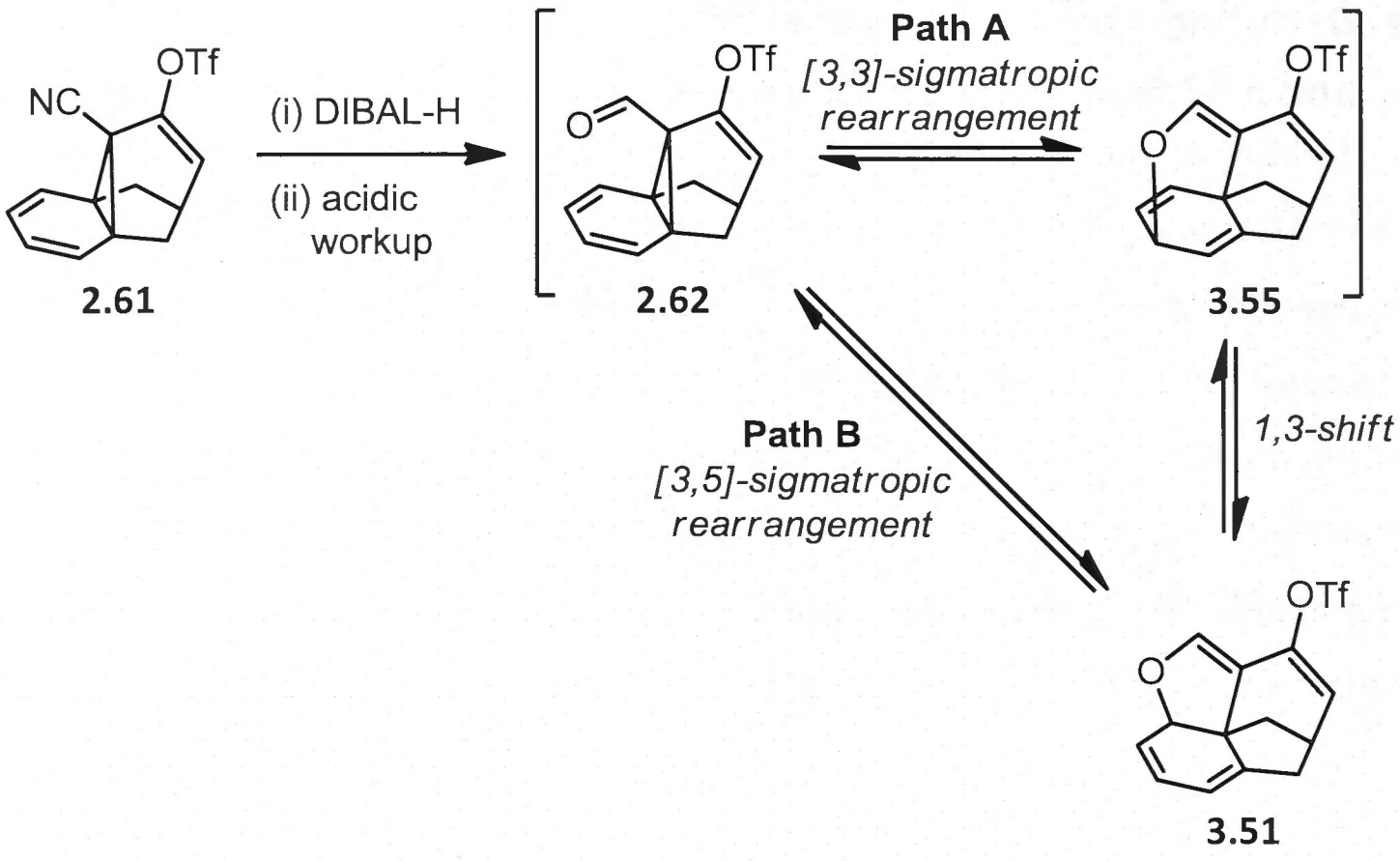
Treating oxa-fenestrane **3.51** with DIBAL-H resulted in formation of alcohol **2.63** and when the latter was oxidised with PCC[13] or TPAP/NMO,[14] then the precursor oxa-fenestrane was regenerated (Scheme 3.14). Such observations, coupled with the outcomes of the Diels-Alder trapping experiments as detailed in Section 3.2.4. above, clearly indicates that these two species are interconvertible through the application of redox processes. This also means that fenestrane **3.51** and aldehyde **2.62** must be in equilibrium with one another. The same situation applies to aza-fenestrane **3.52** because it is in equilibrium with propelladiene **3.54** and the latter, for example, forms the corresponding amine upon reduction with DIBAL-H.



3.51 **2.62** **2.63**

Scheme 3.14. The redox-based interconversion of fenestrane **3.51** and propellane **2.63**.

The formation of the oxa- and aza-fenestranes **3.51** and **3.52** could be explained by either one of two different reaction pathways, as illustrated for the former compound in Scheme 3.15. Thus, either aldehyde **2.63** undergoes a [3,3]-sigmatropic rearrangement, followed by a 1,3-shift (Path A), or it forms the fenestrane directly *via* a [3,5]-sigmatropic rearrangement (Path B). The [3,5]-sigmatropic rearrangement is a symmetry forbidden process under thermal conditions. However, theoretical studies by Houk and co-workers[15] on the hydrocarbon analogue suggested that the reaction proceeds *via* a stepwise diradical mechanism. Studies by Kohmoto *et al.*[16] also indicate that this type of reaction can occur within the norcaradiene framework. On the other hand, a 1,3-shift (as proposed for path A) is not thermally allowed either but could be facilitated by the ring-strain in intermediate **3.55**.

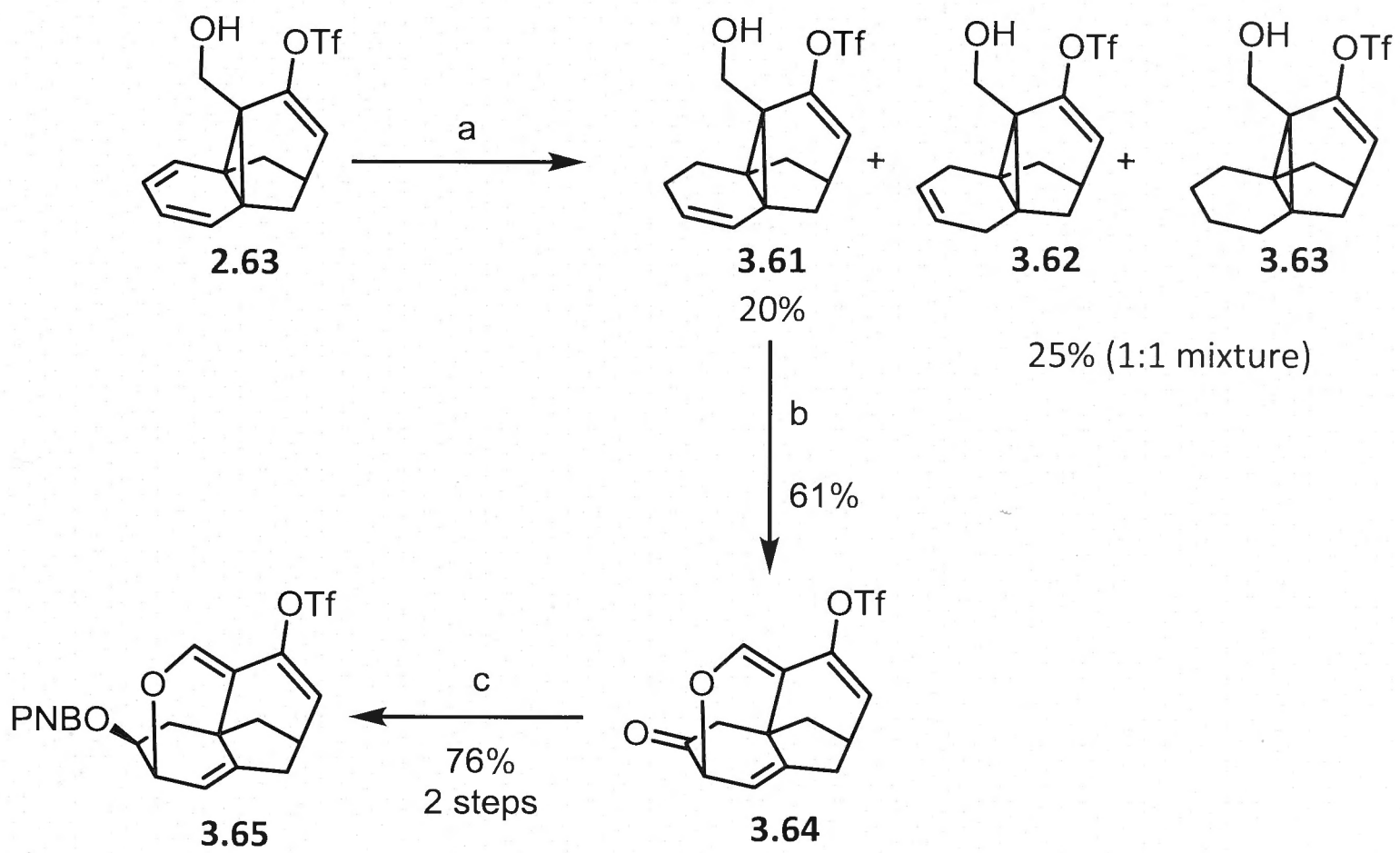


Scheme 3.15. Possible pathways for the rearrangement of aldehyde **2.62** to fenestrane **3.51**.

3.3.1. Experimental Evidence for a Prevalent Rearrangement Pathway

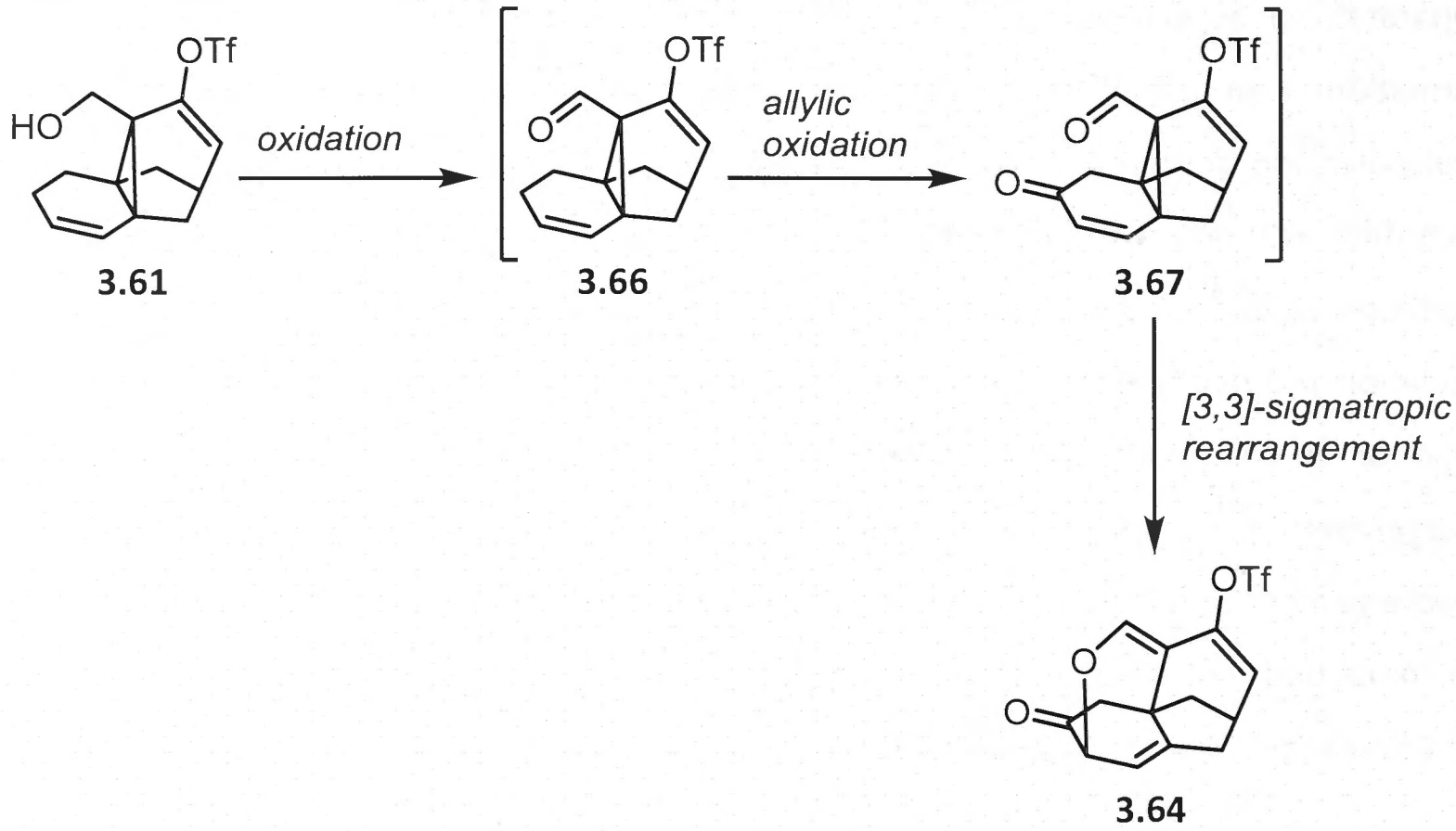
In an effort to identify the pathway(s) by which the fenestranes **3.51** and **3.52** are formed from the precursor nitrile various studies were undertaken. So, for example, to determine whether a [3,3]-sigmatropic rearrangement process was possible it was necessary to prevent the operation of the other pathway and this was achieved through partial hydrogenation of the diene moiety within alcohol **2.63** (Scheme 3.16). The alcohol moiety of the thus formed product would then be oxidised to the corresponding aldehyde. If a reaction did occur after this oxidation step, it would have to be a [3,3]-sigmatropic rearrangement process. In the event, when alcohol **2.63** was subjected to hydrogenation (at atmospheric pressure) in the presence of either palladium on charcoal or rhodium on alumina for ten minutes then a mixture of the desired unsymmetrical alcohol **3.61** (20%), its symmetrical counterpart **3.62** and the over-reduced compound **3.63** was obtained. Due to the short reaction time the outcome of the reaction was strongly dependant on the stirring efficiency as well as hydrogen pressure and the observed yields were quite variable. The desired alcohol **3.61** could be purified by careful column chromatography and the byproducts **3.62** and **3.63** were then separated from one another by column chromatography using silver-impregnated silica gel.[17] However, the attendant time-consuming purification could be circumvented by subjecting the crude mixture of alcohols **3.61**-**3.63** to reaction with PCC in DCM at room temperature since the oxidation products thus obtained proved to be more easily separable. The products of the oxidation of alcohols **3.62** and **3.63** cannot rearrange and so the corresponding mixture of aldehydes **3.62/63** was isolated. However, whether reacted

separately or as a mixture, oxidation of the mono-saturated alcohol **3.61** resulted in the formation of an unexpected product. Mass spectrometric analysis of this product revealed a molecular ion fourteen mass units higher than expected. Ultimately, this product was identified as the fenestrane **3.64** (Scheme 3.16). The same product was obtained when the oxidation of alcohol **3.61** was carried out using TPAP, while use of a Swern[18]- or IBX-based oxidation protocol did not effect any oxidation of the substrate whatsoever. The ^{1}H NMR spectrum of compound **3.64** displayed the same characteristic singlet (at δ 6.61) for an ether-bridge methine hydrogen as observed for oxa-fenestrane **3.51**, suggesting that a similar rearrangement occurred. Unfortunately, a single-crystal X-ray analysis could not be carried out on compound **3.64** as all attempts to crystallise this new fenestrane or various derived esters, including the PNB-ester **3.65**, were unsuccessful.



Scheme 3.16. *Reagents and Conditions*: (a) H_2 (1 atm), Pd-C (2 mol%), EtOAc, rt, 0.17 h; or H_2 (1 atm), Rh-Al_2O_3 (2 mol%), EtOAc, rt, 0.17 h; (b) PCC, DCM, rt, 2 h; (c) i. $CeCl_3$, $NaBH_4$, MeOH; ii. PNB-Cl, DMAP, rt, 1 h.

The conversion **3.61** → **3.64** most likely proceeds as illustrated in Scheme 3.17. Thus, the alcohol moiety within the starting material is first oxidised to the corresponding aldehyde **3.66** but this then undergoes allylic oxidation to give compound **3.67** which engages in a [3,3]-sigmatropic rearrangement reaction to give the observed oxa-fenestrane **3.64**. Of course, the possibility that the allylic oxidation step takes place first cannot be discounted.



3.61 **3.66** **3.67** **3.64**

Scheme 3.17. Proposed mechanism of the formation of fenestrane **3.64** from precursor **3.61**.

3.3.2. Computational Results** [19]

Because the above-mentioned experiments failed to differentiate between the two possible reaction pathways shown in Scheme 3.15, namely between a direct [3,5]-sigmatropic rearrangement and a [3,3]-sigmatropic rearrangement followed by a 1,3-migration process, computational assessments of the energetics of the interconversion of aldehyde **2.62** and fenestratetraene **3.51** were carried out. These were conducted at a high level of theory [G3(MP2)RAD(+) and under "conditions" reflecting the experimental ones, *i.e.* gas phase Gibbs free energies were calculated with G3(MP2)-RAD(+)//B3LYP/6-31+G[d]. Solvation free energies were calculated using the SMD model at the M06–2X/6-31+G(d,p) level of theory in CH_2Cl_2 on solution-phase optimized geometry; the solvation contribution to the reaction energies (at 233 K) was approximated from those obtained at 298 K albeit on compounds (*viz.* compound **3.68**) (Figure 3.6) in which the OTf group was replaced by a hydrogen atom.

2.62 **3.68**

Figure 3.6. The aldehyde **2.62** and its simplified analogue **3.68** used for computational studies.

** Dr. Junming Ho and Prof. Michelle L. Coote are gratefully acknowledged for carrying out the computational calculations presented in this section.

These calculations (Figure 3.7) revealed that the ground state energies of the two compounds were comparable (9.3 kJ mol^{-1} *vs.* 4.9 kJ mol^{-1}) whereas that of compound **3.69** was considerably higher (58.9 kJ mol^{-1}). A qualitatively similar situation was observed for the Me_2HAl-complexed forms of compounds **3.70** and **3.69**, *viz.* the complex of **3.69** was also of higher energy than that of aldehyde **3.68**. It should be stressed that while the calculations presented here indicate that the equilibrium lies in favour of compound **3.68** (with **3.70** being 4.9 kJ mol^{-1} higher in energy), this is entirely due to the model chosen where the OTf group was replaced with a hydrogen atom (so as to reduce the computational cost). Qualitative assessment at a lower level of theory [B3LYP/6-31+G(d)] revealed that inclusion of the OTf group leads to compound **3.70** predominating, an outcome that is consistent with the experimental findings.

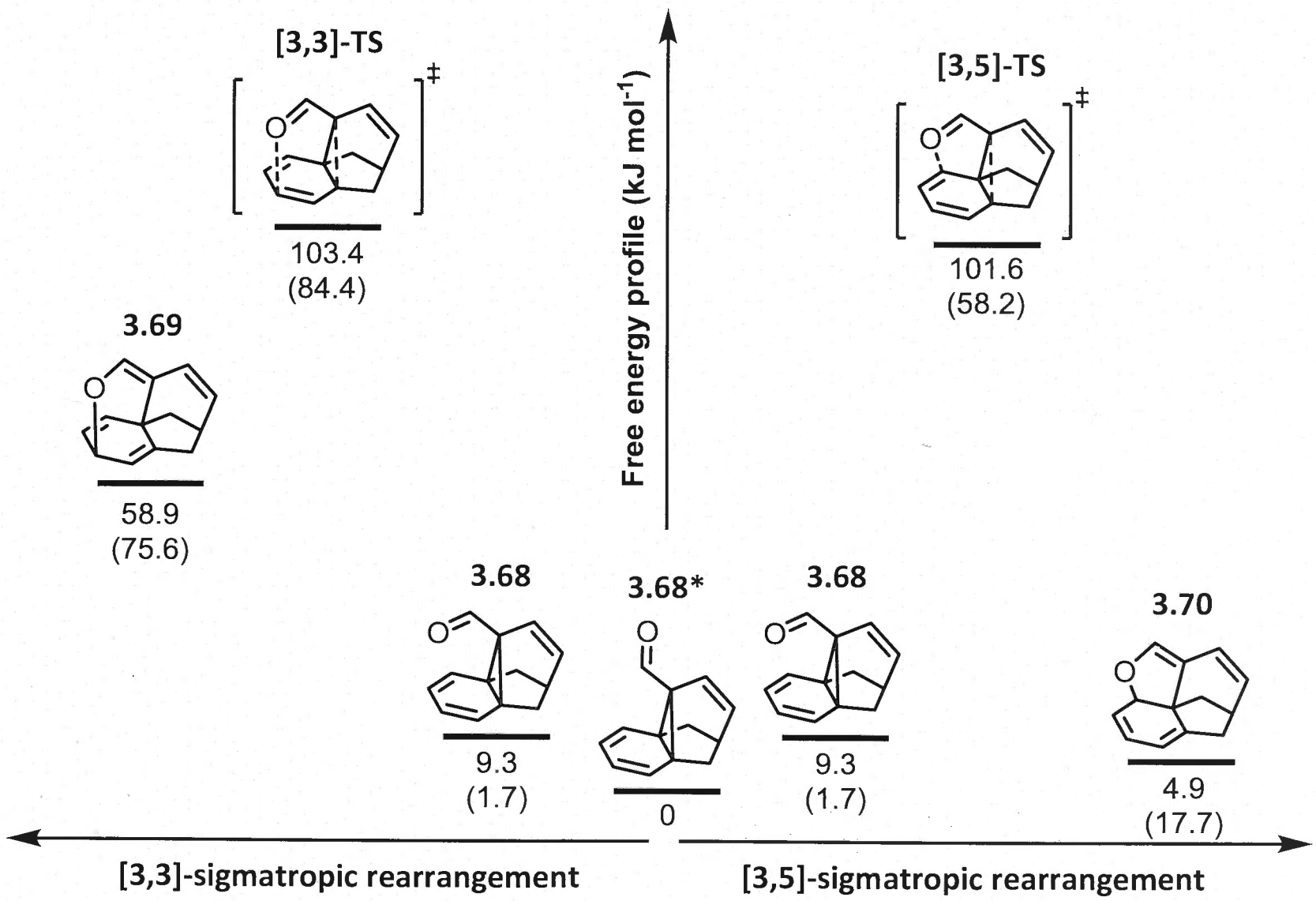


Figure 3.7. Gibbs-free-energy profiles for the [3,5]- and [3,3]-sigmatropic rearrangements of [4.3.1]pro-pelladiene **3.68** in which the OTf group is replaced with a hydrogen atom (the values in parentheses refer to Me_2HAl-complexed analogues while * denotes the lowest energy conformer of aldehyde **3.68**).

The transition states for the conversion **3.68** → **3.70** and the conversion **3.68** → **3.69** were calculated to be of similar energies (101.6 kJ mol^{-1} versus 103.4 kJ mol^{-1}) but very significant

differences were encountered for the corresponding Me_2HAl-complexed compounds (58.2 kJ mol^{-1} versus 84.4 kJ mol^{-1}). The calculated natural-bond-order (NBO) atomic charges and solvation free energies indicate a significantly more polarized transition state in which, for example, the atomic charge on the carbonyl oxygen is 0.024 *e* more negative. These characteristics might account for the different stabilities of the Me_2HAl-complexed transition states. The transition states detected were all closed-shell singlets and various attempts to locate either singlet biradical transition states or intermediates were unsuccessful. This result is unexpected because the [3,5]-sigmatropic rearrangement is thermally disallowed and when it does occur it is thought to proceed through a stepwise pathway involving biradical intermediates.[15] Inspection of the frontier molecular orbitals (Figure 3.8) appears to provide an explanation in that the molecular geometry facilitates overlap between the HOMO (the π orbital of the diene) and the π* orbital of the carbonyl group (CO π *).

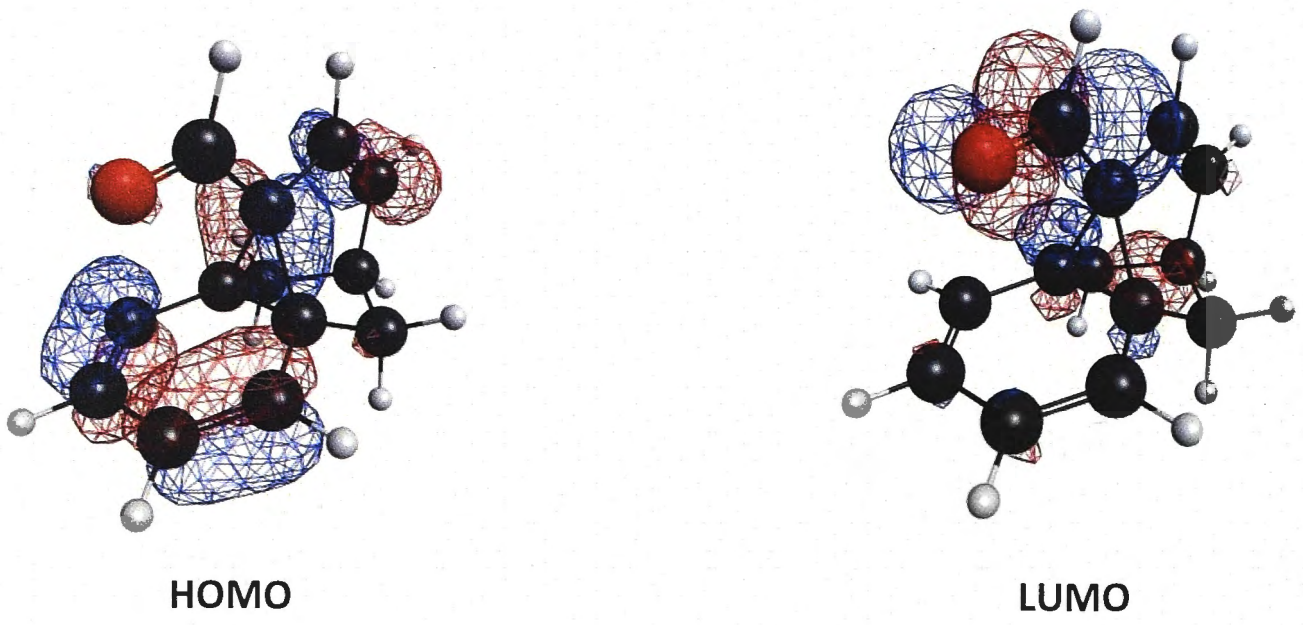


Figure 3.8. Frontier molecular orbitals of intermediate **3.68** (see Scheme 3.15) obtained at the B3LYP/6-31G(d) level of theory.

This overlap results in an activation barrier of approximately 100 kJ mol^{-1}. This is relatively low in comparison to the values that are typical for thermally allowed hydrocarbon-based pericyclic reactions (which have activation barriers of approximately 140 kJ mol^{-1}).[15]

Under the "reaction conditions" used in the computational work (−40 °C), the calculated barriers associated with direct conversion of both aldehyde **3.68** into fenestratetraene **3.70** and aldehyde **3.68** into fenestratetraene **3.69** translate into half-lives of greater than 260 years. By comparison, the corresponding barriers associated with the Me_2HAl-complexed compounds confer half-lives consistent with the time-scale of the actual experiments. On this basis, acid-catalysed [3,5]-sigmatropic rearrangements are believed to be operative in the

conversions of nitrile **2.61** into fenestratetraene **3.70**, alcohol **2.63** into fenestratetraene **3.70**,[††] and fenestratetraene **3.70** into alcohol **2.63**.

3.4. Conclusion

The above-mentioned transformations represent new and unconventional means of generating fenestranes and suggest that oxa- and aza-based variants of the [3,5]-sigmatropic rearrangement could be used for assembling complex heterocyclic frameworks. In light of these results, it is conceivable that the "retro-Claisen" rearrangement product observed during the course of the recently reported total synthesis of salvileucalin B (**1.3**)[20] may result from the operation of a [3,5]-sigmatropic rather than a [3,3]-sigmatropic process.

[††] In the case of this rearrangement we assume the acidic nature of the reaction medium resulting from the presence of PCC facilitates the conversion of aldehyde **3.68** into oxa-[5.6.5.6]fenestratetraene **3.70**.

3.5. References

(1) a) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311; b) Rao, V. B.; Agosta, W. C. *Chem. Rev.* **1987**, *87*, 399; c) Keese, R.; Thommen, M. *Synlett* **1997**, 231; d) Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, 2000; e) Keese, R. *Chem. Rev.* **2006**, *106*, 4787; f) Thommen, M.; Prevot, L.; Eberle, M. K.; Bigler, P.; Keese, R. *Tetrahedron* **2011**, *67*, 3868.

(2) Denmark, S. E.; Montgomery, J. I.; Kramps, L. A. *J. Am. Chem. Soc.* **2006**, *128*, 11620.

(3) Penkett, C. S.; Woolford, J. A.; Day, I. J.; Coles, M. P. *J. Am. Chem. Soc.* **2010**, *132*, 4.

(4) a) Wiberg, K. B.; Wendoloski, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 5679; b) Rao, V. B.; Wolff, S.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1984**, *0*, 293; c) Würthwein, E.-U.; Chandrasekhar, J.; Jenmis, E. D.; von Ragué Schleyer, P. *Tetrahedron Lett.* **1981**, *22*, 843.

(5) a) Georgian, V.; Saltzman, M. *Tetrahedron Lett.* **1972**, *13*, 4315; b) Dauben, W. G.; Walker, D. M. *Tetrahedron Lett.* **1982**, *23*, 711; c) Rao, V. B.; George, C. F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 5732.

(6) a) Wender, P. A.; Dore, T. M.; deLong, M. A. *Tetrahedron Lett.* **1996**, *37*, 7687; b) Penkett, C. S.; Woolford, J. A.; Read, T. W.; Kahan, R. J. *J. Org. Chem.* **2011**, *76*, 1295.

(7) Son, S. U.; Park, K. H.; Chung, Y. K. *J. Am. Chem. Soc.* **2002**, *124*, 6838.

(8) Gaich, T.; Mulzer, J. *Org. Lett.* **2009**, *12*, 272.

(9) Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615.

(10) Yoon, N. M.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443.

(11) Levin, S.; Nani, R. R.; Reisman, S. E. *Org. Lett.* **2010**, *12*, 780.

(12) Rojas, A. C.; Crandall, J. K. *J. Org. Chem.* **1975**, *40*, 2225.

(13) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647.

(14) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(15) Leach, A. G.; Catak, S.; Houk, K. N. *Chem.--Eur. J.* **2002**, *8*, 1290.

(16) Kohmoto, S.; Nakayama, N.; Takami, J.-i.; Kishikawa, K.; Yamamoto, M.; Yamada, K. *Tetrahedron Lett.* **1996**, *37*, 7761.

(17) a) Aitzetmüller, K.; Goncalves, L. A. G. *J. Chromatogr., A* **1990**, *519*, 349; b) Li, T.-S.; Li, J.-T.; Li, H.-Z. *J. Chromatogr., A* **1995**, *715*, 372; c) Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425.

(18) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(19) Heinrich, N.; Willis, A. C.; Cade, I. A.; Ho, J.; Coote, M. L.; Banwell, M. G. *Chem.--Eur. J.* **2012**, *18*, 13585.

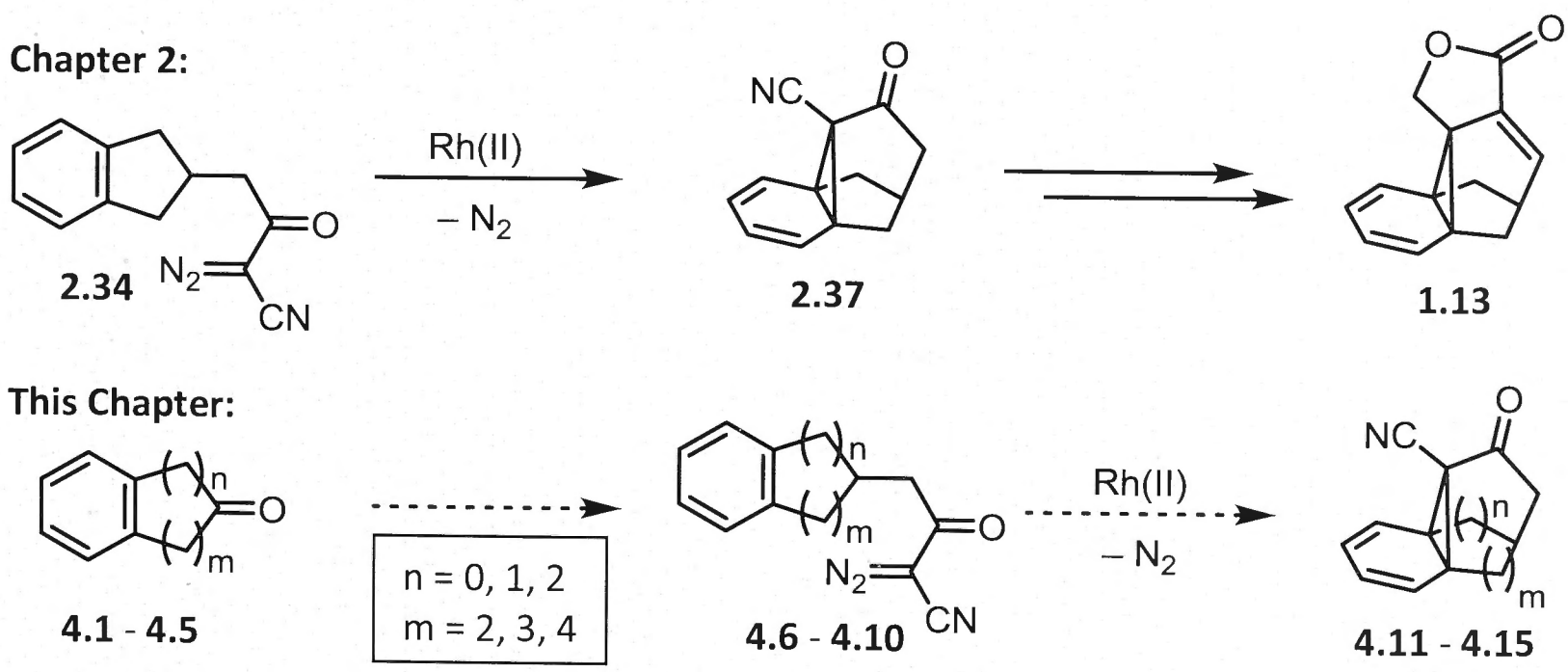
(20) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774.

Chapter 4

Investigating the Scope of the Büchner Reaction as a Means for Generating Salvileucalin B Analogues and Various Fenestranes

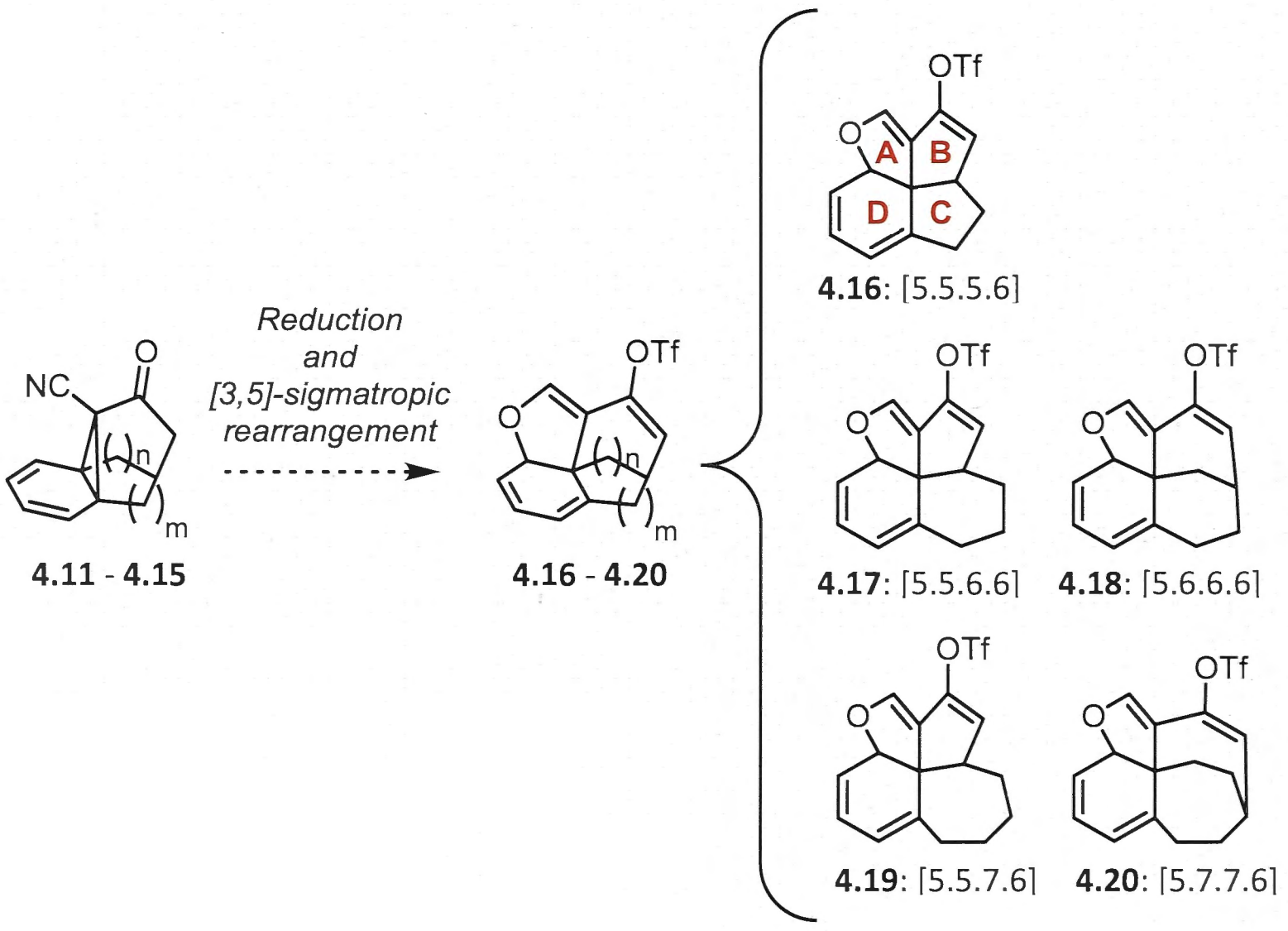
4.1. Overview

Chapter 2 detailed studies that involved applying the Büchner reaction to diazo-β-ketonitrile **2.34** as a means of constructing the norcaradiene substructure associated with the caged core lactone **1.13**. On this basis, it was expected that the related diazo-β-ketonitriles **4.6 - 4.10** (Scheme 4.1) could engage in analogous reactions to give the propelladienes **4.11 - 4.15**, respectively. The motivation for seeking to generate such dienes derived from the possibility that these could serve as building blocks for the assembly of analogues of the lactone **1.13**. Such diazo-β-ketonitriles would need to be prepared from the indanone-analogues **4.1 - 4.5** which vary in the ring-size of the cycloalkanone substructure.



Scheme 4.1. Proposed pathway for the formation of propelladienes **4.11 - 4.15**.

While the metal-catalysed reactions of a wide range of related diazocarbonyl compounds have been investigated[1,2] no systematic study of the effect of ring-size, temperature and catalyst within such systems appears to have been undertaken. The work detailed in the following pages sought to redress this situation. It was thought this chemistry could also provide access to a series of analogues of the aza- and oxa-[5.6.5.6]fenestranes **3.51** and **3.52** described in Chapter 3. Such a series of analogues (see Scheme 4.2) would vary in the size of both the B- and C-rings. Naturally, an interest lay in investigating the geometries of the resulting fenestranes, especially the smallest of the targeted analogues, *viz*. [5.5.5.6]-fenestrane **4.16**, which was expected to embody a larger planarising distortion than the previously synthesised [5.6.5.6]fenestratetraenes.



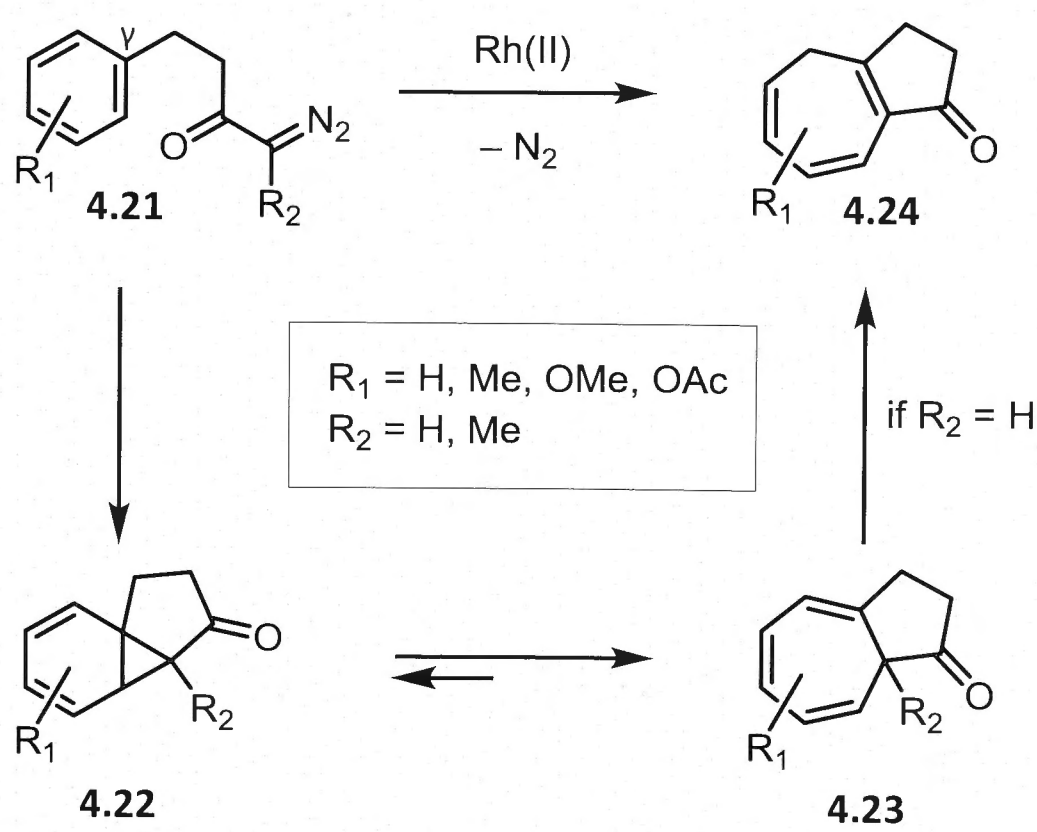
Scheme 4.2. The proposed route to fenestranes **4.16** - **4.20**.

4.2. Chemoselectivity: Büchner *vs*. C-H Insertion Reaction

Büchner and C-H insertion reactions often compete with one another. While numerous studies have been undertaken to investigate the chemo- and regio-selectivity of both types of processes,[3] predicting which will occur in a given system remains difficult and a wide range of factors can influence matters. The main focus of the investigations detailed here included a study of the influence of the length of the tether linking the diazo-moiety and the "reactive site" (*viz*. the proximate sp^2-hybridised carbons of the benzenoid ring),[3c,4] the substituents on the arene ring, neighbouring group effects,[1,3c,4-5] and the nature of the catalyst.[1,3b] Previous studies relevant to such matters are presented in the following sections.

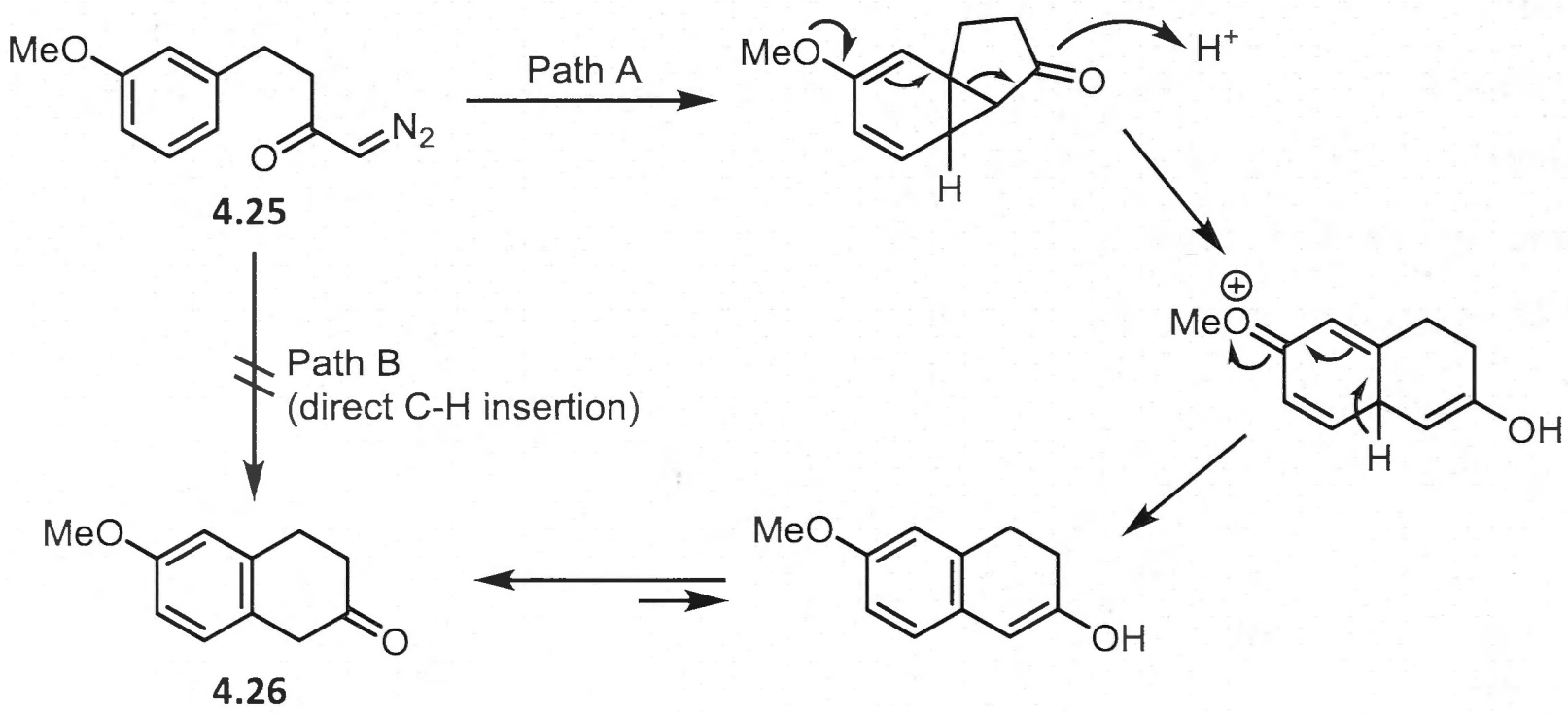
4.2.1. Effects of Tether Length and Arene- and Diazo-Substitution Pattern

Investigations into the rhodium-catalysed decomposition of diazoketone **4.21** and several of its substituted derivatives have been undertaken (Scheme 4.3).[3c,6] The tether between the diazocarbonyl moiety and the pendant aromatic ring was comprised of two methylene groups, meaning that the position gamma to the carbonyl, which is normally the preferred site for C-H insertion, involved a quaternary carbon and so C-H insertion at this position could not take place. As a result, only the Büchner-reaction occurred to give norcaradiene **4.22**, which itself engaged in an electrocyclic ring-opening to give compound **4.23**. In turn, this last compound isomerised to give the more fully conjugated ketone **4.24**.



Scheme 4.3. A Büchner reaction/electrocyclic ring-opening/double-bond migration sequence leading to bicyclo[5.3.0]decatrienones.

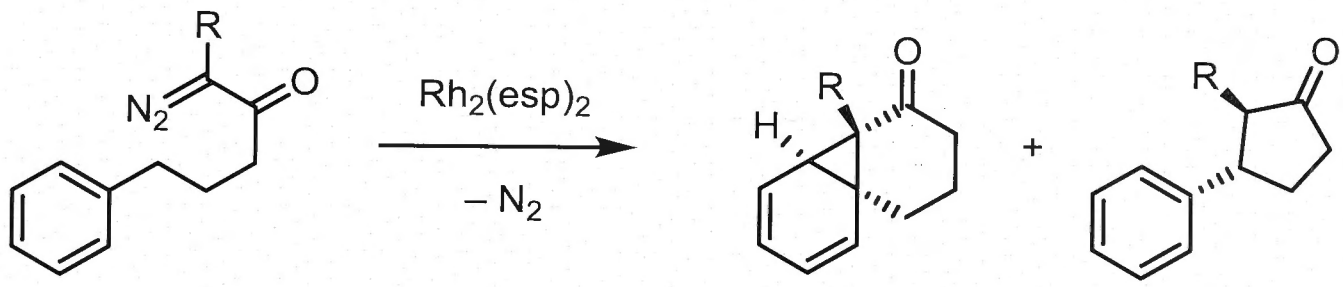
All *para*-substituted systems reacted smoothly, giving the ring-opened products of the general form **4.24**. The presence of *ortho*-substituents caused the Büchner reaction to occur at different sites depending on the precise nature of the substituent. An *ortho*-methoxy group directed the carbenoid addition towards the side of the aromatic ring adjacent to the substituent, while an *ortho*-methyl group had the opposite effect. A *meta*-substitution pattern resulted in different reaction outcomes depending on the nature of the substituent. Interestingly, if a methoxy group was attached at the *meta*-position, as in compound **4.25** (Scheme 4.4), the tetralone **4.26** was obtained and this was believed to be generated by the illustrated pathway A, involving ring-opening of the three-membered ring followed by rearomatisation, rather than *via* Path B involving a direct aromatic C-H insertion process. Similar reactivity for *meta*-substitution patterns has been also observed in studies involving longer tethers between the aromatic ring and the diazoketone moiety.[6b] In an overall sense, then, the Büchner reaction was the sole process operating in all of these systems.[7]



Scheme 4.4. Proposed mechanism for the formation of tetralone **4.26**.

Compounds of the form **4.21** incorporating an α,α-disubstituted diazo-function (e.g. R_2 = Me) also engaged in a Büchner reaction. However, while in these cases rhodium(II)-acetate was ineffective, the use of rhodium(II)-trifluoro acetate or -mandelate allowed for the formation of the Büchner product in quantitative yield.[3c] When the tether length was increased by one methylene unit it was found that the environment about the diazo-moiety began to play a significant role in its reactivity.[3c,6b] So while compound **4.27a** (R = H), which incorporates a mono-substituted diazo-function, engages in a cyclopropanation reaction to give the corresponding Büchner product **4.28a** (Scheme 4.5), compounds containing an α,α-disubstituted diazo-functionality (R ≠ H) undergo a C-H insertion process to form five-

membered rings (**4.29**). It is interesting to note that the nitrile substituted diazoketone **4.27c** (R = CN) presents a unique exception to this rule and engaged in an intramolecular Büchner process to yield the corresponding norcaradiene **4.28c** as the only isolable product (Table 4.1).[6b]



4.27 a-f **4.28 a-f** **4.29 a-f**

Scheme 4.5. Influence of the substitution at the diazo-group on the chemoselectivity of the ensuing carbene. (Note: The abbreviation "esp" stands for the bidentate tetramethylated *m*-benzenediproprionic acetate ligand developed by Espino *et al.*[8])

Table 4.1. The Influence of the Diazo-Substitution on Chemoselectivity.[6b]

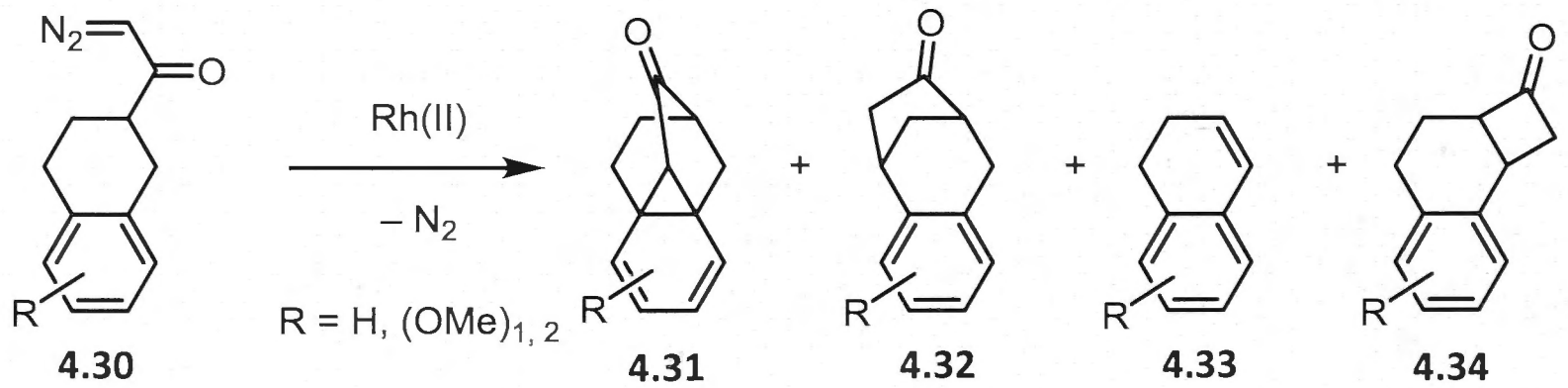
Starting Material 4.27	**Diazo-Substituent (R)**	**Yield**	
		4.28	**4.29**
a	H	> 95%	-
b	Me	-	43%
c	CN	70%	-
d	COMe	-	32%
e	CO_2Me	-	45%
f	NO_2	-	28%

Most likely, this outcome is attributable to steric effects. Potentially, the second substituent at the carbon bearing the diazo-moiety could interfere with the alignment of the arene π-system with the initially-formed rhodium carbenoid. Certainly, the relatively small sizes of the nitrile and hydrogen are consistent with this explanation. Kennedy's[3c] investigations into the chemoselectivity of methyl-substituted diazoketone **4.27b** (R = Me) showed that even in the presence of Rh(II)-mandelate, a catalyst usually favouring the Büchner reaction, this compound only underwent an aliphatic C-H insertion process to give the corresponding cyclopentanone derivative **4.29b**.

When the tether connecting the aromatic ring to the diazocarbonyl unit was increased by one or two additional methylene units,[3c] C-H insertion was observed even for mono-substituted

diazocarbonyls. In such systems the aromatic ring was simply too far removed from the diazo-function to react competitively. Naturally enough, when the tether was eight atoms or longer the regioselectivity of the metal-catalysed decomposition processes of diazocarbonyl compounds showed strong similarities to those of the equivalent intermolecular cyclopropanation reactions.[5a,9]

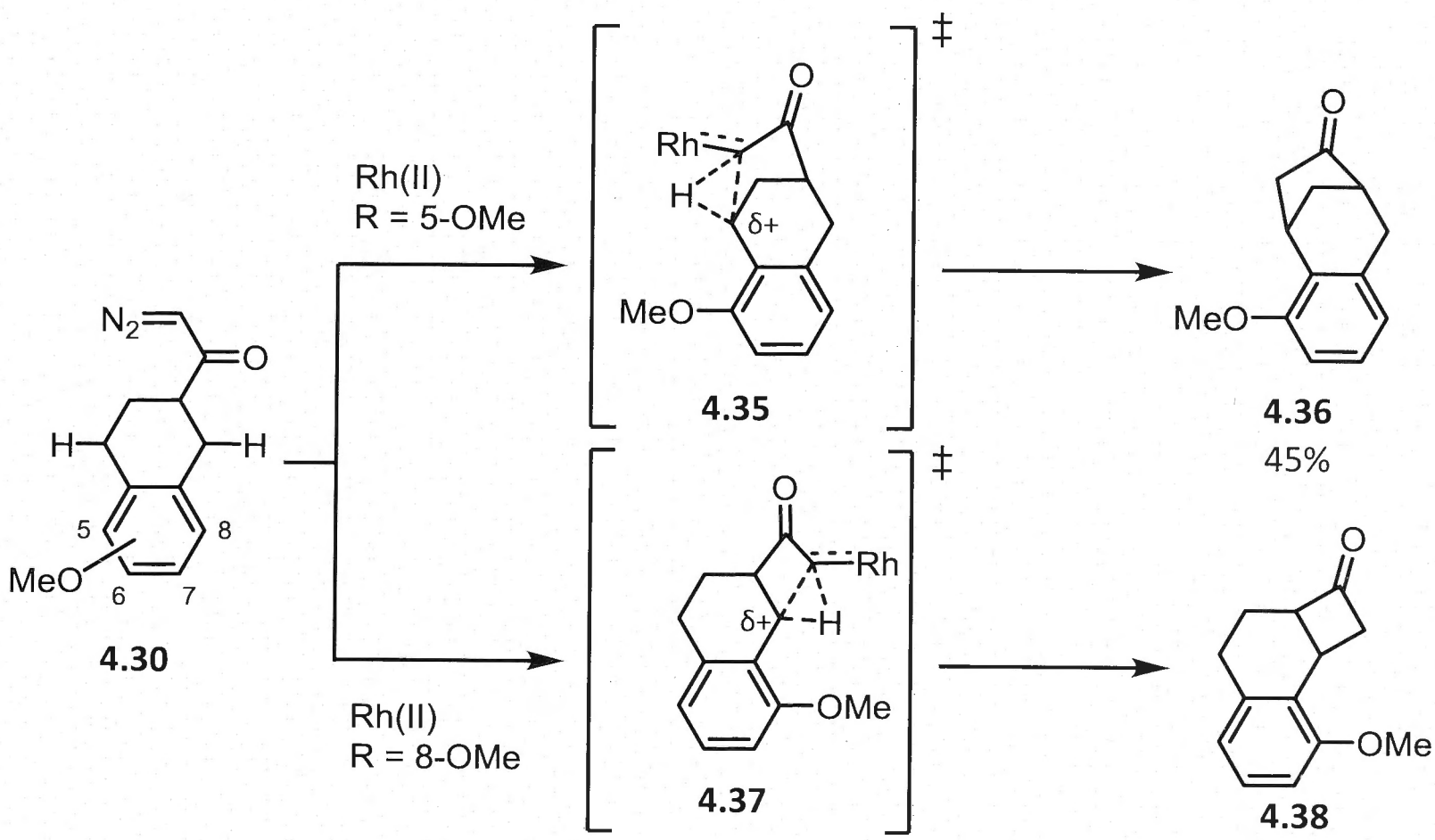
If the tether connecting the arene and diazocarbonyl moieties is part of a ring system[1] then the Büchner reaction continues to compete with C-H insertion processes. So, for example, the unsubstituted Büchner precursor **4.30** (R = H) (Scheme 4.6) showed little selectivity between aromatic cyclopropanation and aliphatic C-H insertion and thus products **4.31** (R = H) and **4.32** (R = H) were obtained in similar yields. Co-products **4.33** and **4.34** (R = H) also appeared to be obtained albeit in < 10% yield in each case. Methoxy-substituents [R = $(OMe)_n$, n = 1, 2] in different positions on the aromatic ring affected the ratio of compounds **4.31** and **4.32**, and in the case of the 6,8-dimethoxy-substituted substrate a fragmentation product, **4.33** [R = $(OMe)_2$], was even obtained (in 20% yield).



Scheme 4.6. Products formed in the Rh(II)-catalysed decomposition of diazoketones of the general form **4.30**.[1]

It was expected that the placement of one or more methoxy-substituents on the arene ring would increase the electron density of the aromatic ring and thus promote formation of the desired norcaradiene. Surprisingly, however, C-H insertion into both benzylic positions occurred and thus leading to compounds **4.32/4.34** (R = OMe) and **4.36/4.38**. This regioselectivity could be explained through the involvement of a three-centre transition state[10] in which the C-C bond being formed is polarised towards the electron-poor carbenoid (Scheme 4.7). On this basis, the introduction of methoxy-substituents at C5 or C7 of the substrate would be expected to stabilise the partial positive charge and thus activate it towards C-H insertion reactions that pass through a transition state of the form **4.35**,[11] this selectivity being favoured not only because of the activating effect of the methoxy-substituents but also because five-membered ring formation is favoured on entropic grounds. Indeed, the major product is the

tricyclic ketone **4.36**. When substrates incorporate a methoxy group at C8 then insertion into the alternative benzylic position could take place *via* a transition state of the form **4.37** and thus leading to the generation of small amounts of the cyclobutanone-containing compound **4.38**.[1]



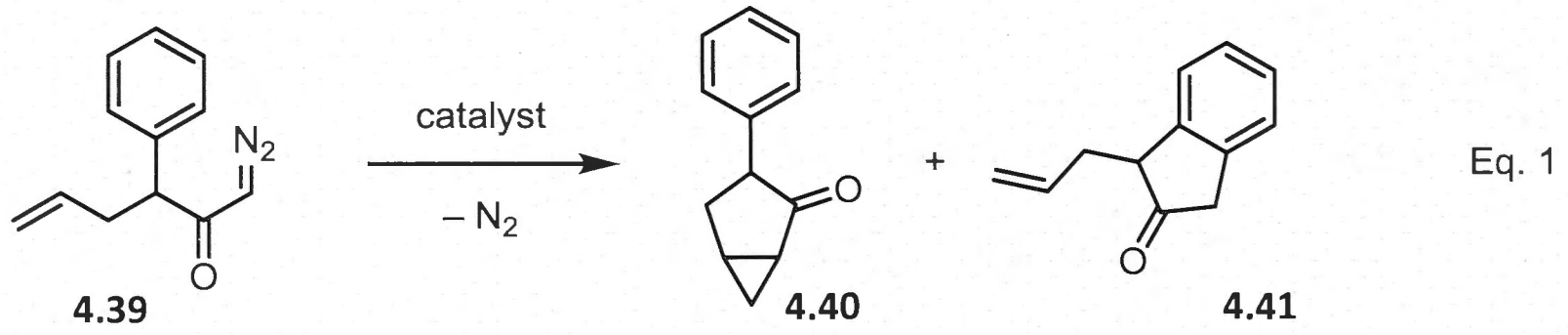
Scheme 4.7. Reactions indicating that methoxy-substituents facilitate C-H insertion into the benzylic positions.

Surprisingly, however, varying amounts of compounds of the general form **4.32** (R = H or OMe) were present in all product mixtures of all substitution patterns, and small amounts of compound **4.34** were also observed for the unsubstituted substrate **4.30** (R = H). These results demonstrate the highly variable nature of C-H insertion processes and the significant role that both kinetic and electronic effects can play in them.

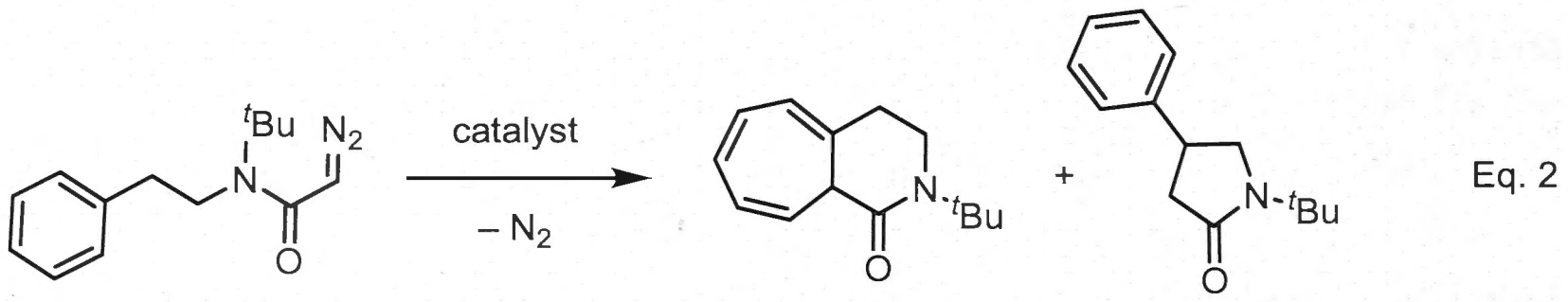
4.2.2. The Effect of Catalysts on the Outcome of Reactions

While copper-based catalysts have been successfully used to effect both Büchner and C-H insertion reactions,[12,13] rhodium(II)-based species seem to be the most commonly used for these types of transformation.[3c,14] Padwa and Doyle *et al.*[3b] have shown that the choice of ligand associated with the central metal atom has a great impact on the reactivity of the resulting carbenoid. Scheme 4.8 shows, by way of illustration, two reactions that were carried out in the presence of the four catalysts listed in Table 4.2. Thus, when diazoketone **4.39** was

subjected to reaction with rhodium acetate, cyclopropane **4.40** and the indanone derivative **4.41** were isolated in comparable yields (Eq. 1 and Table 4.2, entry 1). The introduction of additional substituents on the C-C double bond within compound **4.39** had a negligible impact on the ratio of the products obtained. Similarly, competition between aromatic cyclopropanation and C-H insertion (Eq. 2) showed only a slight preference for the formation of products (*e.g.* **4.43**, entry 1) arising from a Büchner reaction pathway. However, using rhodium perfluoroborate (pfb) (entry 2) resulted in the exclusive formation of the aromatic C-H insertion product **4.41** and, in the case of the second substrate (**4.42**), increased selectivity for aromatic cyclopropanation to give compound **4.43**. This selectivity could be completely reversed when rhodium caprolactam (cap) (entry 3) or rhodium acetamidate (acam) (entry 4) were used.



4.39 **4.40** **4.41**



4.42 **4.43** **4.44**

Scheme 4.8. Ligand effects on the chemoselectivity.

Table 4.2. Relative Yields Obtained in Padwa's Catalyst-Dependent Selectivity Study.[3b]

Entry	**Catalyst**[a]	**Relative Yields of Products 4.40, 4.41, 4.43 and 4.44**			
		4.40	**4.41**	**4.43**	**4.44**
1	$Rh_2(OAc)_4$	45	55	68	32
2	$Rh_2(pfb)_4$	0	100	95	3
3	$Rh_2(cap)_4$	100	0	3	97
4	$Rh_2(acam)_4$	NA	NA	23	77

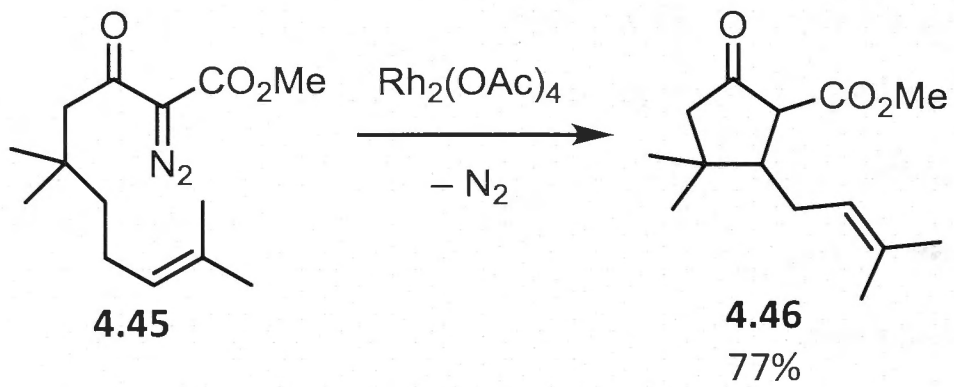
[a] Ligands: OAc = acetate, pfb = perfluoroborate, cap = caprolactam, acam = acetamidate; NA: data not available.

As a general rule, ligands incorporating electron-withdrawing residues such as perfluoroborate or trifluoroacetate produced a more electrophilic carbenoid such that the reactivity preference was in the order aromatic substitution > tertiary CH-insertion > cyclopropanation (aliphatic ~ aromatic) > secondary CH-insertion. In contrast, using electron-donating ligands such as caprolactam and acetamidate resulted in a less electrophilic species and as a result the reactivity profile was aliphatic cyclopropanation > tertiary CH-insertion > secondary CH-insertion > aromatic cycloaddition. Usefully, rhodium acetate provides a carbenoid somewhere in between these two extremes. In retrospect, then, it is perhaps surprising that rhodium acetate provided the best results in effecting the conversion of compound **2.34** to **2.37** described in Chapter 2 when, instead, rhodium trifluoroacetate would be expected to favour aromatic cyclopropanation, rather than facilitating the formation of a byproduct resulting from a C-H insertion process.

4.3. Regioselectivity

4.3.1. Intramolecular C-H Insertion

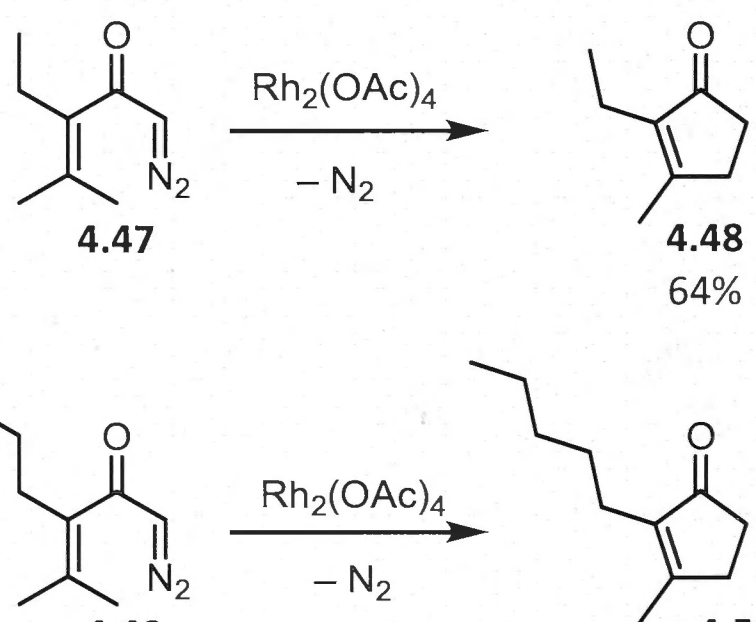
The most characteristic feature of the intramolecular C-H insertion reactions being considered here is that formation of five-membered rings is strongly favoured. In cases where more than one C-H bond is in the γ-position relative to the carbonyl moiety, then there is a distinct preference for insertion into a C-H bond attached to a more substituted carbon. Benzylic and allylic positions are less susceptible to carbenoid insertion and this is presumed to be the result of inductive effects. So, while alkyl groups have a positive inductive effect, by increasing electron density at the C-H bond and so facilitating attack of the electrophilic metal-carbenoid species, allylic and benzylic groups exert a negative inductive effect and thus making the adjacent C-H bond less susceptible to insertion.[3a,15] For example, when subjected to reaction with rhodium acetate, compound **4.45** (Scheme 4.9), which contains three possible sites for γ-C-H insertion, *viz*. one methylene and two methyl groups, reacts *via* methylene C-H insertion to give cyclopentanone **4.46** even though, statistically speaking, the methyl groups would have been favoured all other things being equal.



4.45 **4.46**
77%

Scheme 4.9. Preferential formation of the methylene C-H insertion product **4.46** (over methyl insertion products) from compound **4.45**.

Such outcomes stand in some contrast to the work by Wenkert *et al.*[16] who reported that when compound **4.47** was treated with rhodium acetate then the cyclopentanone **4.48** resulting from C-H insertion into the proximate methyl group was the major product of the reaction (Scheme 4.10, Eq. 1). When the length of the aliphatic side chain was increased so that a methylene or methine unit was present in the γ-position, as seen in substrate **4.49**, then the reaction lead to a 1:1 mixture of the two insertion products, namely compounds **4.50** and **4.51** (Scheme 4.10, Eq. 2).



4.47 **4.48**
64%

Eq. 1

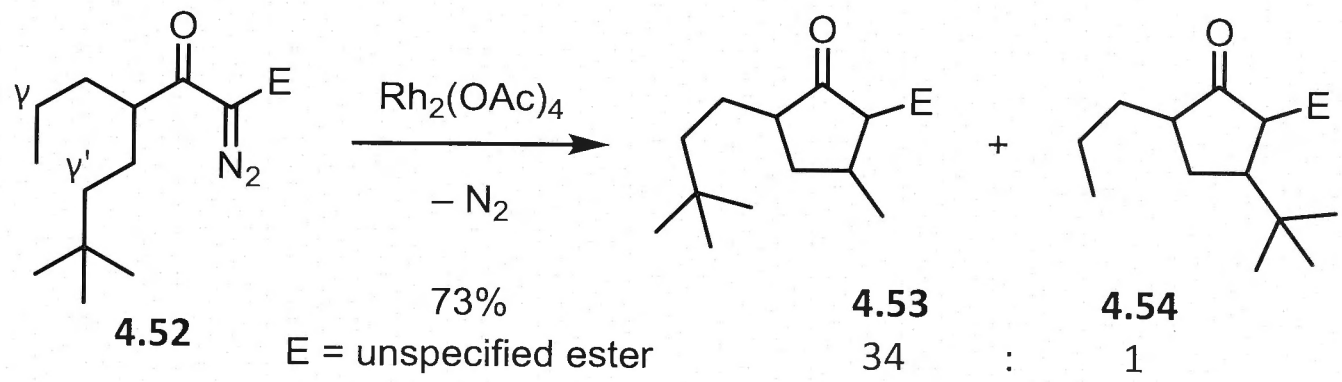
4.49 **4.50** **4.51**
80% 1 : 1

Eq. 2

Scheme 4.10. Conversions highlighting the competing C-H insertion pathways leading to cyclopentenones.

These somewhat opposing outcomes have been rationalised by invoking an initial and readily reversible precomplexation of the metal-carbenoid to the C-H bond[3a], which allows the thermodynamically more stable product to be formed. The lack of selectivity observed in Wenkert's experiments can be attributed to endocyclic C-C double bonds being more stable than exocyclic ones, thus making insertion into the usually disfavoured allylic C-H bond a much more competitive process in this instance.

Factors other than electronic ones can also influence the regioselectivity of the C-H insertion process.[3a] Thus, when both γ-positions are "occupied" by methylene groups, with one having an adjacent methyl group and the other a similarly located *tert*-butyl group (as seen in substrate **4.52** for example) then, as shown in Scheme 4.11, a 34:1 mixture of products **4.53** and **4.54** is obtained with the former product predominating due to preferential insertion at the less hindered γ-position.



Scheme 4.11. The influence of steric bulk on the regioselectivity of the C-H insertion process.

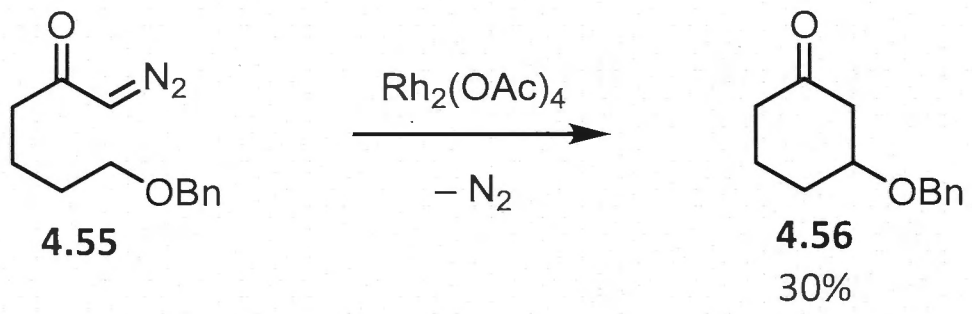
Such steric effects also become apparent when comparing relative ratios of methylene- *vs.* methyl-insertion with methylene- *vs.* methine-insertion processes. Taber[3a] showed that the first of these types of competition yields only the methylene insertion product. In the latter type of competition a mixture of both insertion products is observed although methine insertion is favoured to some extent.

4.3.2. The Stereoselectivity of the C-H Insertion Process

It has been established that C-H insertion reactions proceed with retention of configuration,[17] and thus allowing for stereoselective processes to be undertaken in certain instances. So, for example, Taber and co-workers found that C-H insertion into open chain systems often proceeds with a high degree of diastereoselectivity to form five-membered ring products in which there was a *trans*-relationship between the substituents.[18] An analogous assessment involved substrates incorporating cycloalkanes and thus leading to bicyclic systems.[3a] When a cyclopentane was involved then only the *cis*-fused bicyclic product was obtained. With higher homologues both *cis*- and *trans*-fused products were isolated with the latter isomeric form predominating. However, through the use of different catalysts the selectivity of such processes could be adjusted to some extent. Asymmetric C-H insertion processes, including those leading to the formation of quaternary carbon centres[19] and heterocycles,[5b] have been achieved using chiral catalysts.

4.3.3. Neighbouring Group Activation

As mentioned in Section 4.3.1., substituents such as benzyl- or allyl-moieties deactivate methylene groups towards C-H insertion. Similarly, even remotely located esters and ketones can diminish the reactivity of a given C-H bond.[20] On the other hand, certain other substituents, especially heteroatoms located alpha to the C-H bond undergoing insertion, can have an activating effect.[21] This preference has been exploited in generating otherwise less accessible four- and six-membered rings.[14] As shown through a study conducted by Adams,[22] upon exposure of diazo-compound **4.55** to a rhodium-catalyst this underwent intramolecular insertion into the C-H bond adjacent to the ether oxygen and thus generating a six-membered ring in preference to the normally formed cyclopentane (Scheme 4.12). Indeed, compound **4.56** was formed as the only isolable product of reaction.



4.55 **4.56** 30%

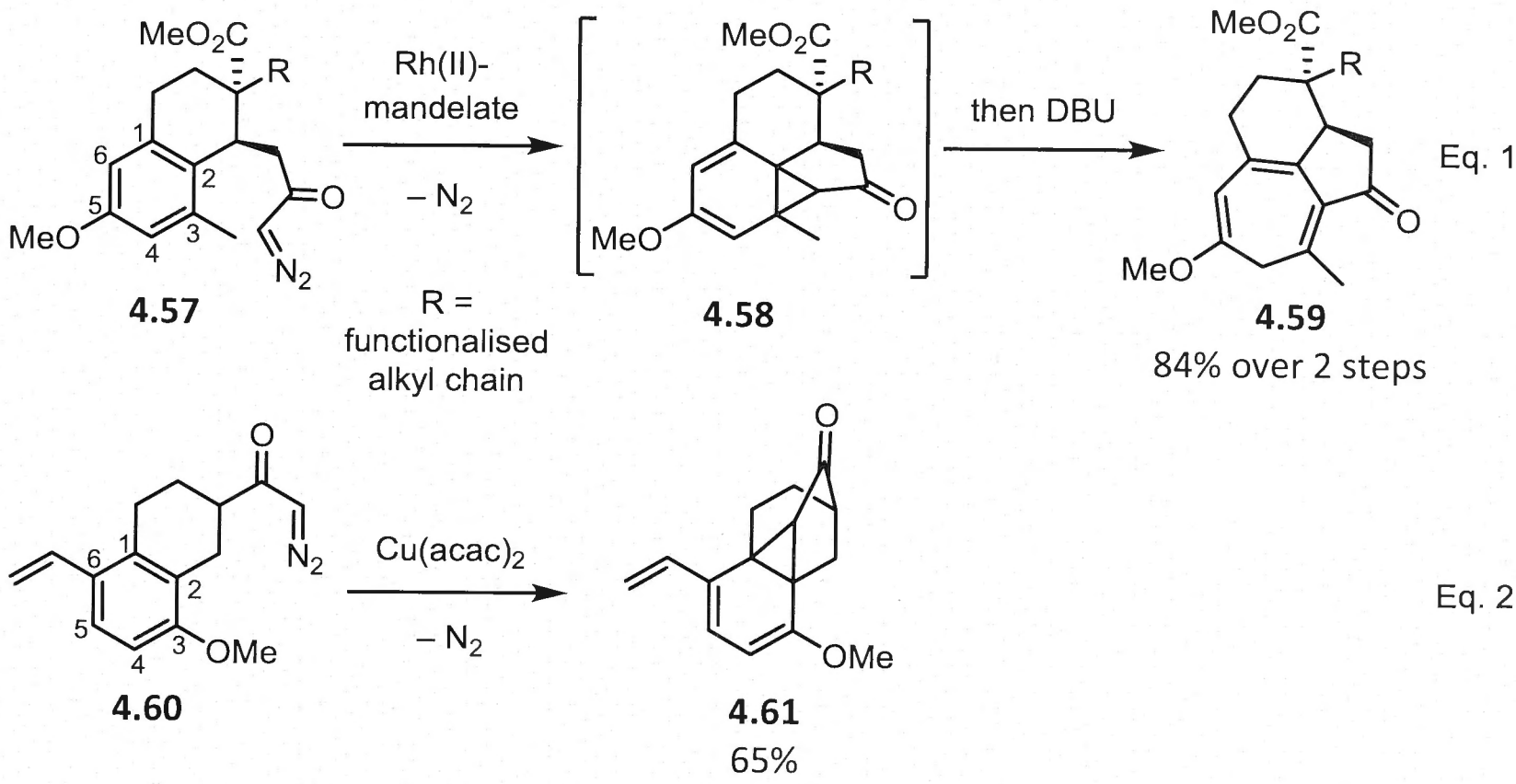
Scheme 4.12. The activating effect of heteroatoms in the position alpha to a C-H insertion site.

4.3.4. The Intramolecular Büchner Reaction

The factors influencing the regioselectivity of the intramolecular Büchner reaction are not as diverse as those that impact on the C-H insertion process, if only because there are usually less sites available for such a reaction. As expected for electron-deficient Fisher-type carbenes, the preferred site of attack is at the most electron-rich region of the aromatic ring unless steric factors overwhelm such a pathway. As described in Section 4.2.1, McKervey and Maguire found that when a simple methylene tether was used to link the carbenoid to the aromatic ring, then the reaction usually occurred at the position remote from methyl, methoxy or acetoxy substituents.[3c,7]

Mander's investigations into such issues of selectivity in decalin-containing systems (Scheme 4.13) showed that both aromatic cyclopropanation (*via* a Büchner process) of the most substituted site,[1] as well as addition to the adjacent site were possible.[2,23] So, for example, in the presence of a rhodium(II)-catalyst, compound **4.57** (Eq. 1) undergoes Büchner reaction involving C2 and C3 to give (presumably) the [3.6.6.5]fenestrane **4.58** that itself undergoes *in situ* electrocyclic ring-opening to form the more stable cycloheptatriene **4.59**. The boat-like

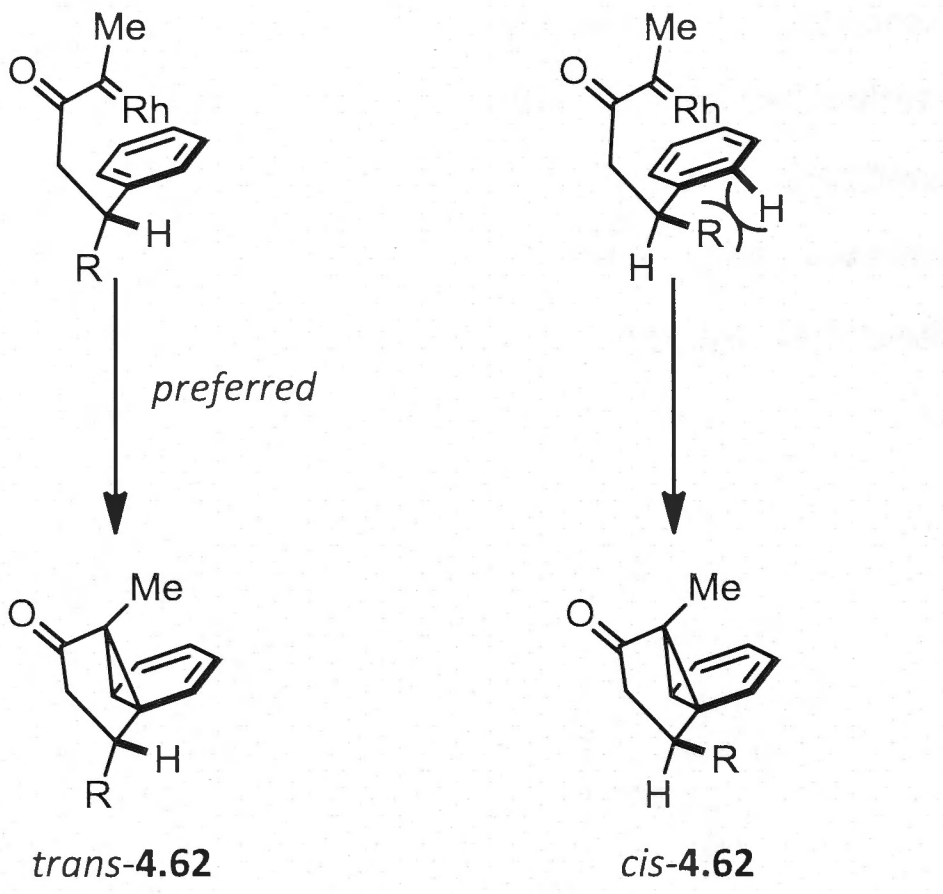
conformation associated with the cyclohexane ring of substrate **4.57** undoubtedly restricts the "range" of the tether and such that the carbenoid arising from the diazoketone attacks at C2/C3 rather than C1/C2. On the other hand, copper-catalysed decomposition of the methoxy-substituted decalin derivative **4.60** (Eq. 2) led to the exclusive formation of the bridged [4.4.1]propelladiene **4.61**. No products arising from alternate modes of cyclopropanation were observed.



Scheme 4.13. The influence of substituents on the outcomes of the intramolecular Büchner reaction.

4.3.5. Stereocontrol in the Intramolecular Büchner Reaction

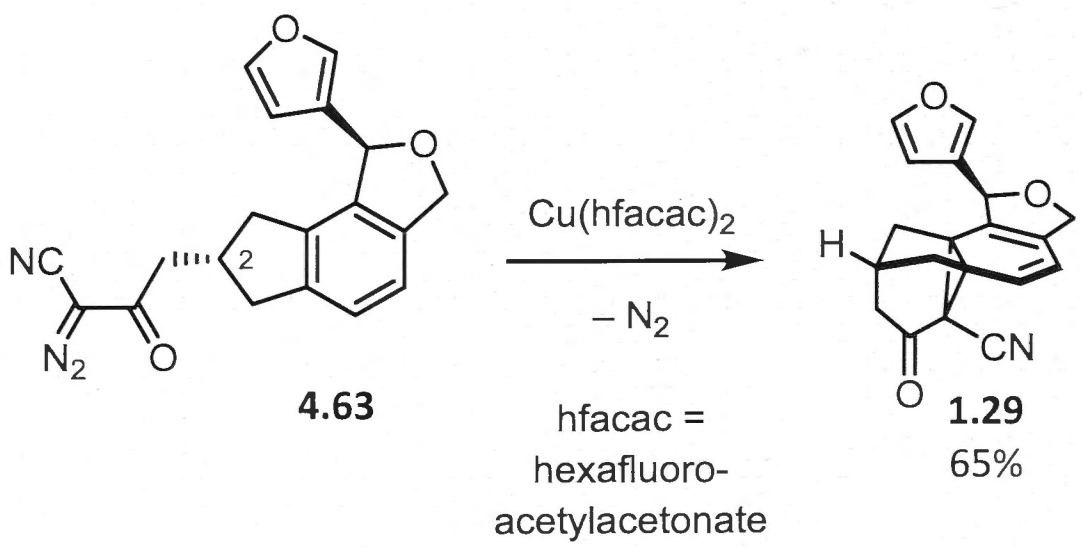
In certain instances highly stereoselective reactions have been observed during the course of the intramolecular Büchner reaction.[24] For example, Maguire *et al.*[24a] have shown that an alkyl group adjacent to the aromatic ring can induce a high degree of diastereoselection. Thus, the formation of compound *trans*-**4.62** is favoured over its *cis*-counterpart *cis*-**4.62** by a factor of 97:3 (Scheme 4.14). This outcome is attributed to unfavourable steric interactions at the transition state for the process leading to the latter diastereoisomer.



trans-**4.62** *cis*-**4.62**

Scheme 4.14. Model for the rationalisation of the observed stereoselectivity in a Büchner reaction involving a non-hydrogen substituent at the benzylic position of the tether.

A related process of diastereoselection in the Büchner reaction (Scheme 4.15) has been exploited by the Reisman group in the total synthesis of salvileucalin B (Chapter 1, Scheme 1.3).[24b] In this case, it was not the substituents on the tether or pendant aromatic ring, but the stereochemistry at C2 of the cyclic tether that allowed the carbenoid to preferentially attack just one side of the aromatic ring and thus inducing stereoselectivity. Specifically, then, the Cu(II)-catalysed decomposition of diazo-β-ketonitrile **4.63** resulted in formation of [4.3.1]propelladiene **1.29** as a single diastereomer.



Scheme 4.15. The pivotal and highly diastereoselective Büchner reaction employed in Reisman's total synthesis of salvileucalin B (**1.3**).

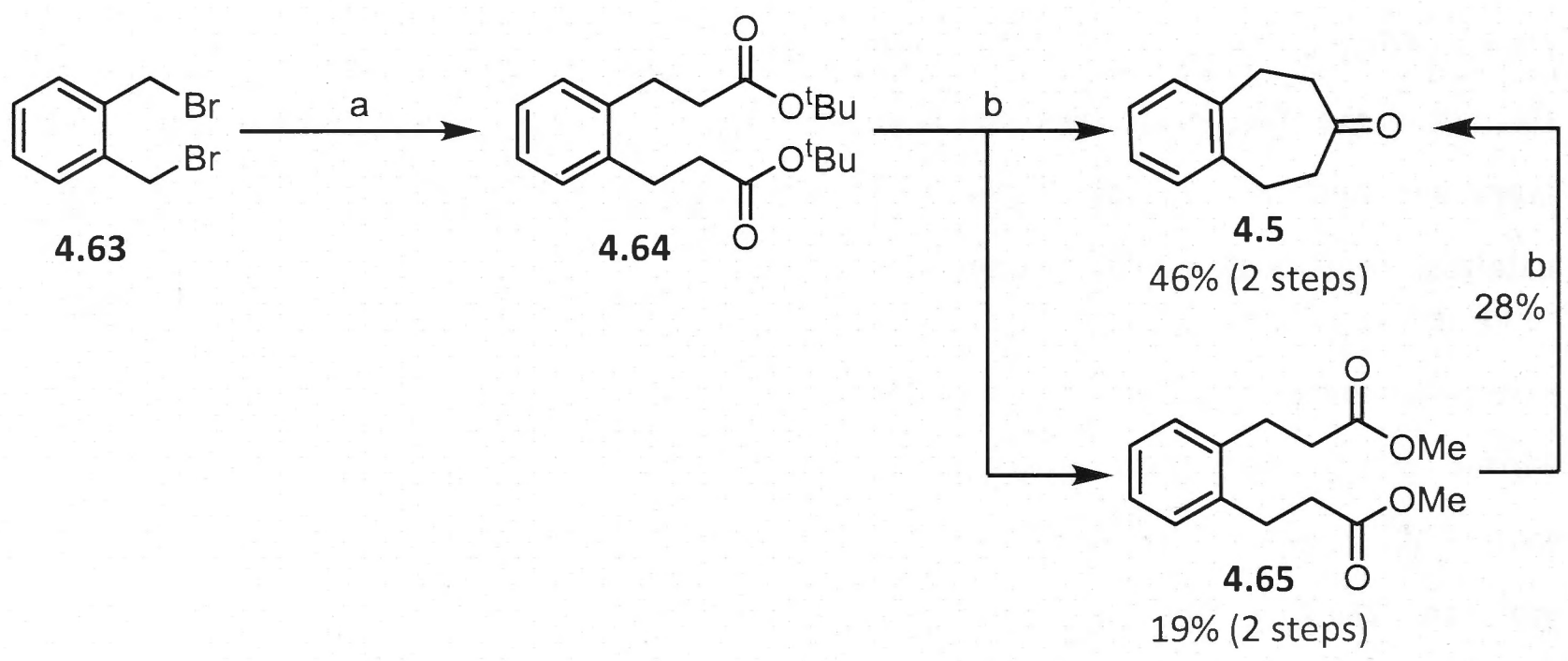
4.3.6. Conclusion

Numerous and often delicately balanced factors govern the outcome, particularly carbenoid addition *vs*. C-H insertion, of the metal-mediated decomposition of α-diazocarbonyl-containing C-C unsaturated compounds. The literature shows that the maximum tether length between the diazoketone and aryl residue that still allows the Büchner reaction to occur efficiently is three carbons in length. If such a tether is incorporated within a ring system, then the prospects for competing C-H insertion reactions increase. Methoxy-substituents on the aromatic ring increase electron density and, therefore, the propensity for engagement of the substrate in a Büchner reaction of one sort or another. Electron-donating groups in the α-position increase the rate of C-H insertion while electron-withdrawing substituents have the opposite effect. Most importantly, the chemoselectivity (cyclopropanation *vs*. C-H insertion) as well as stereoselectivity (especially of the latter process) can be greatly influenced by the choice of ligand associated with the catalyst.

Despite all the detailed studies that have been carried out to date the fine balance between steric and electronic effects still makes it difficult to predict the outcome of any given metal-catalysed reaction of α-diazocarbonyl-containing compounds.

4.4. Synthesis of the Büchner Precursors

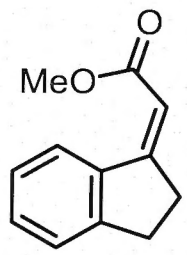
Bearing the background knowledge delineated above in mind, the synthesis of the substrates required to study the variations in the Büchner reaction defined at the beginning of this Chapter were carried out using the relevant cyclic, aromatic ketones as starting materials. All ketones were commercially available except for 3-benzosuberone (**4.5**). This was synthesized according to a procedure reported by Paquette[25] (Scheme 4.16) and obtained in a yield of 46% over the two steps involved. Small amounts of the diester **4.65** were also obtained as a result of a *trans*-esterification reaction taking place during the workup associated with the second step. This by-product could be "recycled" to give additional quantities of the desired 3-benzosuberone **4.5**.



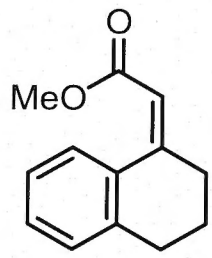
4.63 **4.64** **4.5** 46% (2 steps) **4.65** 19% (2 steps)

Scheme 4.16. *Reagents and Conditions*: (a) *N*-isopropylcyclohexylamine, *n*-BuLi, *t*-butyl acetate, THF, −78 °C to rt, 22 h; (b) i. NaH, *t*-BuOH; ii. glacial HOAc, toluene, reflux, 6 h.

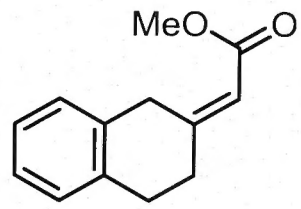
In the first step of the parallel reaction sequences used to generate the substrates for the Büchner reactions under study, ketones **4.1** - **4.5** were each subjected to reaction with the anion derived from trimethyl phosphonoacetate in THF at 0 °C and for the non-benzylic ketones **4.3** and **4.5** the corresponding methyl esters, **4.68** and **4.70** respectively (Figure 4.1), were isolated in good yield. The analogous reaction of the conjugated ketones 1-indanone (**4.1**), 1-tetralone (**4.2**) and 1-benzosuberone (**4.4**) proved to be more sluggish and significant quantities of the starting materials were normally recovered. Such low reactivity could be attributed to the carbonyl function being conjugated to the aromatic ring and thus possessing reduced electrophilic character. In an effort to increase the yields of compounds **4.66**, **4.67** and **4.69** (Figure 4.1) various reaction conditions were tested but only modest improvements in outcome were realised (Table 4.3).



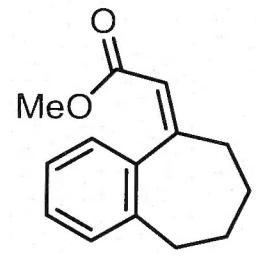
4.66



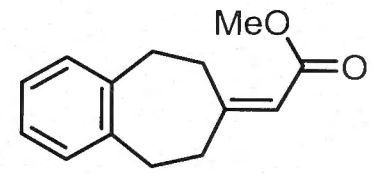
4.67



4.68



4.69



4.70

Figure 4.1. Products obtained from the HWE reaction of ketones **4.1** - **4.5** with trimethyl phosphonoacetate.

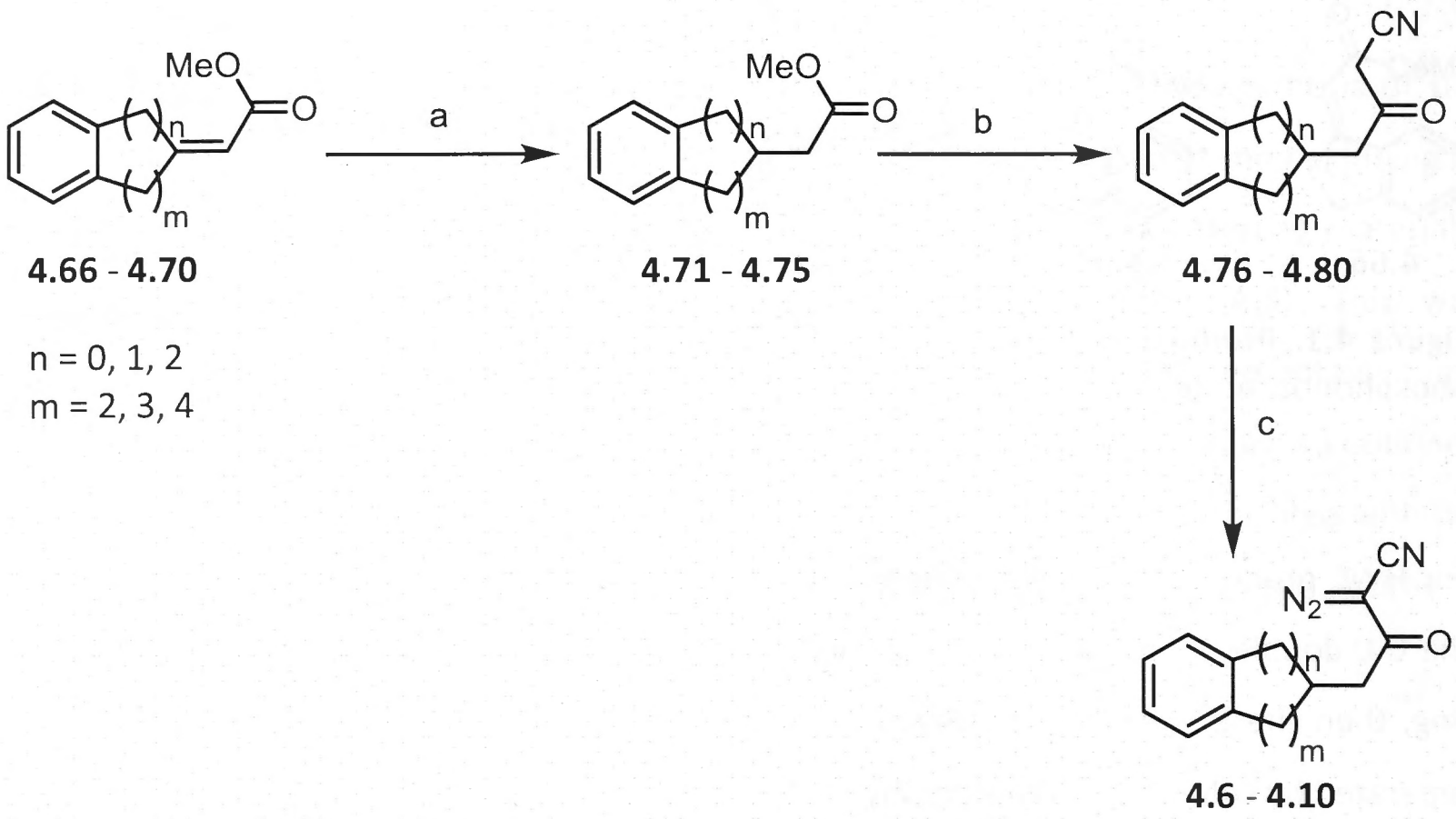
For HWE products that could isomerise to the corresponding β,γ-unsaturated esters wherein the C-C double bond was now in an endocyclic position and in conjugation with the aromatic ring, then these were also observed as co-products.[26,27] Such isomeric compounds could be separated by column chromatography for the purposes of characterisation. Fortunately, as the next step in the reaction sequence was the hydrogenation of the olefinic residue, these mixtures of products were inconsequential in terms of securing the required substrates for the proposed studies of the Büchner reaction.

Table 4.3. Outcomes of the HWE Reactions of Ketones **4.1** - **4.5**.

Staring Ketone	Product Methyl Esters	Reaction Time	Yield	Isomers[c]
1-Indanone (4.1)	**4.66**	21 h[a]	55% (brsm)	(*exo* : *endo*) 1 : 5
1-Tetralone (4.2)	**4.67**	21 h[b]	66% (brsm)	(*exo* : *endo*) 1 : 5
2-Tetralone (4.3)	**4.68**	1.5 h[a]	96%	(*exo* : *conjug. endo*) 1 : 95
1-Benzosuberone (4.4)	**4.69**	21 h[a]	82% (brsm)	(*E* : *Z*)[28] 1 : 3.5
3-Benzosuberone (4.5)	**4.70**	1.5 h[a]	98%	-

[a] *Reagents and Conditions*: Trimethyl phosphonoacetate, NaH, THF, 0 °C to rt; [b] *Reagents and Conditions*: Trimethyl phosphonoacetate, NaH, DMSO, 0 °C to rt; [c] Ratio calculated from the ^{1}H NMR spectra.

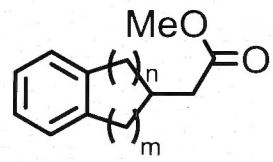
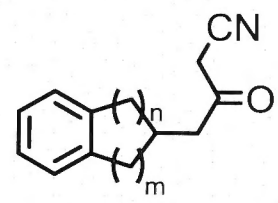
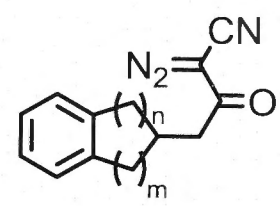
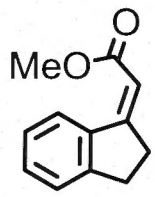
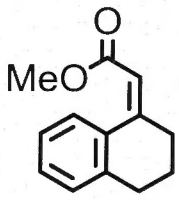
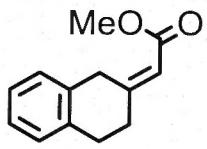
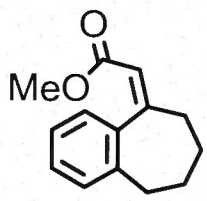
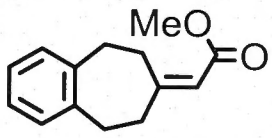
The pathway used to carry forward the products of the HWE reactions is shown in Scheme 4.17 and the outcomes of each reaction are presented in Table 4.4. Thus, the unsaturated esters **4.66** - **4.70** were each readily hydrogenated using 1 atm of hydrogen gas in the presence of 5-6 mol% of 10% Pd on C. The reactions were normally complete after 1.5 h and provided the corresponding saturated esters in good to excellent yields.



Scheme 4.17. *Reagents and Conditions:* (a) H_2, 10% Pd-C, EtOAc, rt, 1 h; (b) MeCN, LiHMDS, THF, −78 °C, 21 h; (c) imidazole sulfonylazide, pyridine, MeCN, 40 °C, 22 h.

In order to prepare the β-ketonitriles **4.76** - **4.80**, the hydrogenated esters **4.71** - **4.75** were each subjected to reaction with the anion derived from acetonitrile and so effecting a nucleophilic addition/elimination reaction and thus generating the required compounds. Yields were only moderate for the esters derived from 1- and 2-tetralone (**4.72** and **4.73**, respectively), but excellent for the other three substrates. Only in the case of the ester **4.74** did the reaction fail to go to completion. This was due to incomplete deprotonation of the acetonitrile as a result of using low quality LiHMDS. However, sufficient material was still obtained by this means to allow the final target compound to be acquired.

Table 4.4. Yields for the Hydrogenation, Nucleophilic Addition and Diazo-Transfer Reactions Shown in Scheme 4.17.[a]

Starting α,β-Unsaturated Ester	Hydrogenation Product 	Nucleophilic Addition Product 	Diazo-Transfer Product 
 (m=2, n=0)	99% **(4.66)**	92% **(4.71)**	78% **(4.6)**
 (m=3, n=0)	57% **(4.67)**	67% **(4.72)**	24% **(4.7)**
 (m=2, n=1)	83% **(4.68)**	66% **(4.73)**	78% **(4.8)**
 (m=4, n=0)	91% **(4.69)**	99% (brsm) **(4.74)**	89% **(4.9)**
 (m=n=2)	68% **(4.70)**	99% **(4.75)**	75% **(4.10)**

[a] Yields are unoptimised.

The diazo-function required in the final compound of the reaction sequences was introduced using a modification of a protocol reported by Goddard-Borger[29] and employing freshly made imidazolesulfonyl azide in the presence of pyridine. The desired diazo-β-ketonitriles **4.6** - **4.10** were obtained as bright-yellow compounds (some oils, some crystalline) in good yields, with the exception of compound **4.7** which, following the consistent trend of all its precursors throughout the reaction sequence, was obtained in low yield (24%). All the spectral data obtained for these diazo-β-ketonitriles were in accord with their assigned structures. Most notably, while the relevant carbon resonances were not detected in the ^{13}C NMR spectra, the IR spectrum of each compound displayed strong C=N=N stretching bands at around 2129 cm^{-1}.

4.5. Reaction of the Diazo-β-Ketonitriles 4.6 - 4.10 with Metal-Complexes

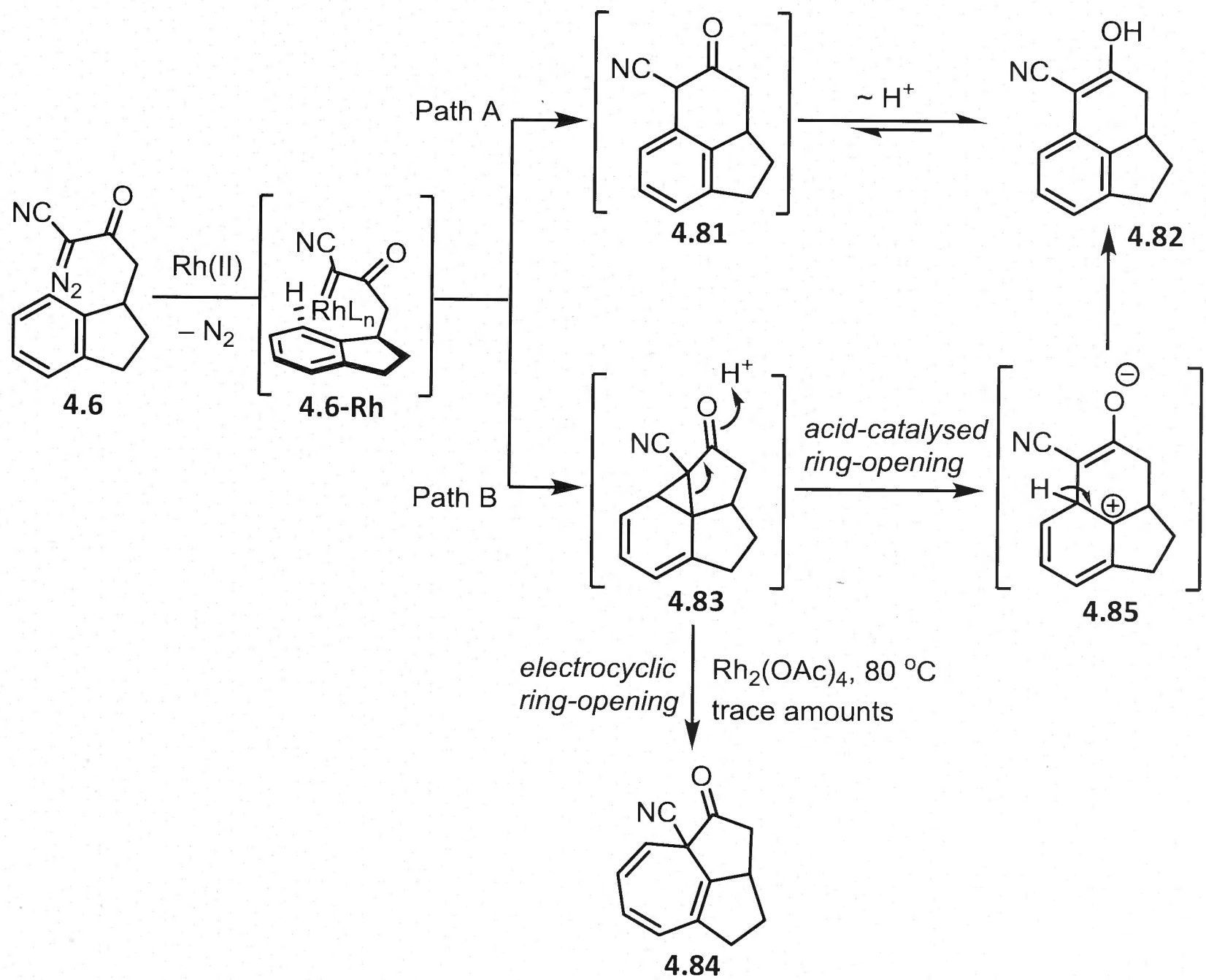
The diazo-β-ketonitriles **4.6** - **4.10** obtained by the means detailed above were each subjected to two distinct sets of reaction conditions (in an effort to effect the desired Büchner reaction), namely using a microwave heating method and a so-called slow addition method. The microwave method was simply used to screen different catalysts and reaction temperatures and conducted on very small scales. Different catalysts were used to establish a chemoselectivity profile (*viz*. cyclopropanation *vs*. C-H insertion). While a catalyst loading of 1 mol% would normally be sufficient for ensuring the reactions go to completion, during these small-scale screening runs a catalyst loading of around 5-10 mol% (*ca*. 1 mg) was usually employed. The solvent of choice was DCM for those reactions conducted at 40 - 50 °C while DCE was used for reactions conducted at higher temperatures. The slow addition method, which was carried out at 80 °C, was used for larger scale reactions (involving *ca*. 0.2 mmol of substrate) and provided better indications of the likely true yields of products obtained.

For screening purposes, four commonly used catalysts were chosen, *viz*. $Cu(acac)_2$, $Cu(tfacac)_2$, $Rh_2(OAc)_4$ and $Rh_2(tfa)_4$. Under the conditions defined above $Cu(acac)_2$ either failed to effect any reaction at all or produced complex mixtures of products while $Cu(tfacac)_2$ showed similar reactivity to $Rh_2(OAc)_4$, but with strongly reduced selectivity. As a result, both of these copper-based catalysts were excluded from further testing. For both rhodium-based catalysts gas-evolution was observed at room temperature, but heating was required to ensure the reactions went to completion in under 2 h.

4.5.1. Reaction of the α-Diazo-β-Ketonitrile 4.6 Derived from 1-Indanone

For the first screening $Rh_2(OAc)_4$ was used as the catalyst because it had successfully effected the Büchner reaction for the symmetrical diazoketone **2.34** derived from 2-indanone (**2.6**) (see Chapter 2). Thus, when diazoketone **4.6** was exposed to this catalyst in DCM at 40 °C in a microwave reactor (2 min ramp, 1 min hold) a new product formed rapidly but ^{1}H NMR analysis of the crude reaction mixture suggested that it was not the desired Büchner product. Chromatographic purification of the reaction product led to the isolation of a crystalline material that was subjected to the usual range of spectroscopic analyses. These allowed for the structural elucidation of compound **4.82** which was later confirmed by single-crystal X-ray analysis. The likely C-H insertion pathway leading to the formation of this material is shown in Scheme 4.18. When the reaction was heated to 80 °C (2 min ramp, 2 min hold) under microwave conditions, enol **4.82** was again found to be the major product. However, the presence of four signals in the alkene region (at δ 6.5, m/ 6.51, d/ 6.1, d/ 5.9, m) of the ^{1}H NMR spectrum of the crude material suggested a trace of co-product **4.84** was present. This would

be formed through a Büchner reaction at the undesired aromatic site to give fenestrane-type intermediate **4.83**, followed by electrocyclic ring-opening to form cycloheptatriene **4.84**. Disappointingly, all attempts to isolate and purify this product were unsuccessful. The reaction was repeated at 120 °C (2 min ramp, 1 min hold) in DCE so as to establish if an increase in reaction temperature would improve the yield of Büchner product **4.84**. However, the ^{1}H NMR spectrum of the crude reaction mixture obtained under such conditions showed that enol **4.82** was the major product and that not even a trace of the Büchner compound **4.84** had been formed in this instance.

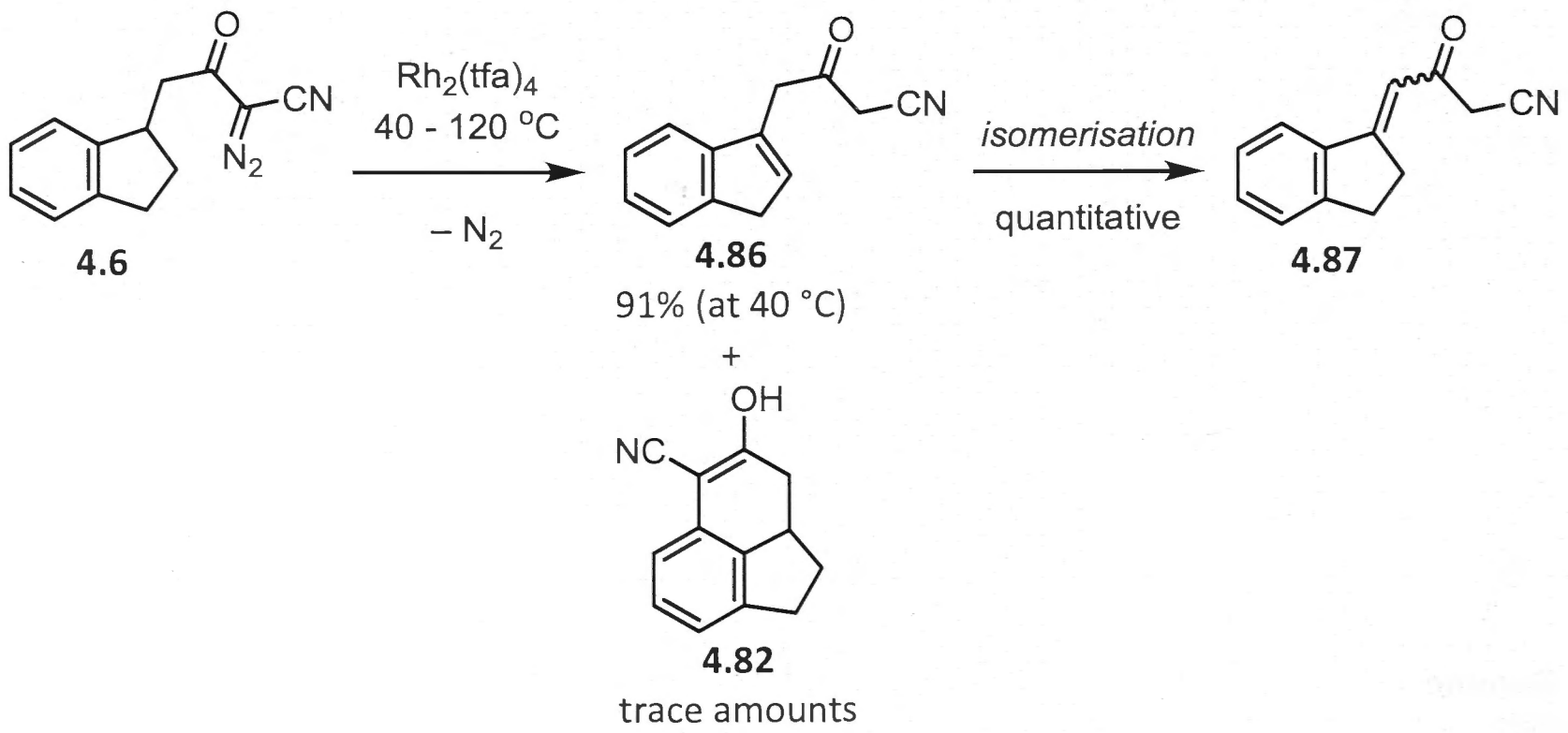


Scheme 4.18. Outcomes of the Rh(II)-catalysed decomposition of diazo-β-ketonitrile **4.6**.

There are at least two possible mechanistic pathways that could be invoked to explain the formation of the fused tricyclic product **4.82**. These are shown in Scheme 4.18. The first (Path A) involves C-H insertion of the metal-carbenoid into the proximate aromatic C-H bond and with the primary product of this process, namely compound **4.81**, then tautomerising to enol **4.82**. On the other hand, the rhodium carbenoid **4.6-Rh** seems perfectly aligned to engage in a Büchner reaction (Path B), resulting in the formation of the strained tetracycle **4.83**. As

suggested[7] for a similar system (see Scheme 4.4), in the presence of acid the three-membered ring associated with product **4.83** could cleave and after proton loss from the Wheland-type intermediate **4.85** compound **4.82** could be formed. Precisely which of these pathways is followed remains unclear at the present time.

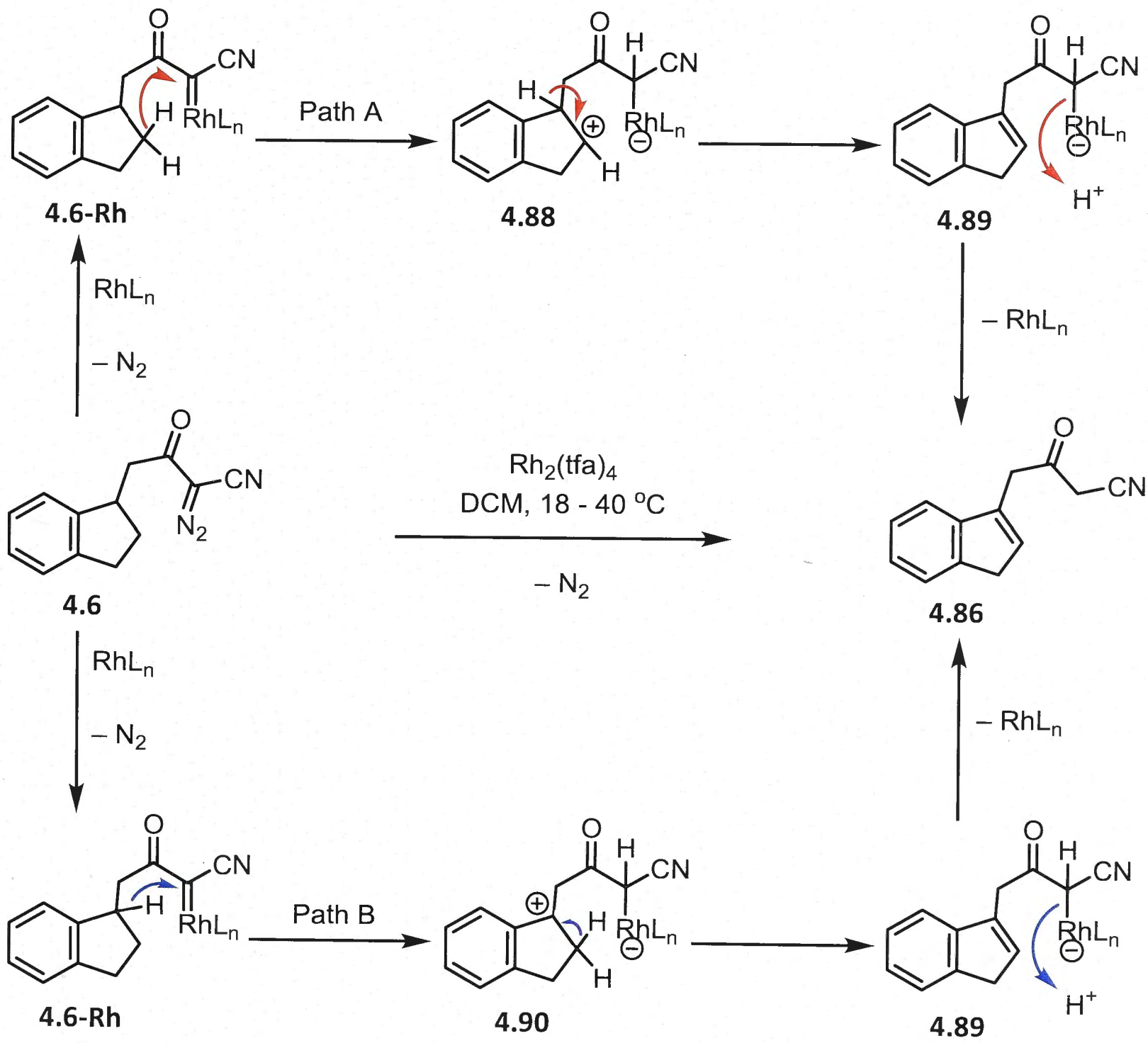
$Rh_2(tfa)_4$ proved to be a useful catalyst for the present purposes and on being used led to complete consumption of the starting material **4.6**. At 40 or 80 °C (2 min ramp, 2 min hold) the reaction yielded only a trace of enol **4.82** with compound **4.86** being the major product of reaction. Heating the substrate to 120 °C (2 min ramp, 1 min hold) slightly increased the proportion of product **4.82** but congener **4.86** still predominated by a factor of two. Again, no trace of the hoped-for Büchner product was observed. The ^{1}H NMR spectrum of this new compound (**4.86**) showed three methylene singlets, and a signal due to a methine proton appeared at δ 6.53, data that did not match those expected for any C-H insertion products. The complete rearrangement of this material on prolonged standing to give the more extensively conjugated **4.87** clearly suggested that the primary product of reaction was indene **4.86** (Scheme 4.19). While compound **4.87** was obtained as a single diastereomer the stereochemistry (*E* or *Z*) of it could not be established.



Scheme 4.19. Outcomes of the $Rh_2(tfa)_4$-catalysed decomposition of diazo-β-ketonitrile **4.6**.

Two possible pathways leading to the formation of compound **4.86** from precursor **4.6** are shown in Scheme 4.20. Thus, β-ketonitrile **4.86** could be generated *via* an initial hydride shift[21,30] involving the rhodium carbenoid to form, by way of intermediate **4.88**, indene **4.89** (Path A). This sort of "anomalous C-H insertion" process has been observed when an adjacent

heteroatom is present to stabilise the cationic intermediate but not otherwise.[21,31] In this first path indene **4.89** then undergoes proteolysis of the Rh-H bond to form the observed product **4.86**. Another possible route to compound **4.86** involves hydride abstraction at the benzylic position (Path B) to give the benzylic cation **4.90**. Intermediate **4.90** would then suffer proton loss to form indene **4.89** which would, in turn, engage in the same demetallation process proposed as part of Path A and so delivering β-ketonitrile **4.86**. Whether the geometric constraints that would apply in the conversion **4.6-Rh** → **4.90** actually preclude the operation of this process is unclear at the present time.



Scheme 4.20. Possible pathways for the formation of indene **4.86** from precursor **4.6**.

The outcomes of applying the abovementioned reaction conditions, as well as some minor variants, to an exploration of the reactivity of substrate **4.6** are presented in Table 4.5. Broadly speaking, not only did the choice of catalyst influence the selectivity of these reactions but the use of higher temperatures also appeared to favour the aromatic C-H insertion process leading

to enol **4.82**. The temperature-dependant chemoselectivity observed in the present case is novel and remains unexplained at the present time.

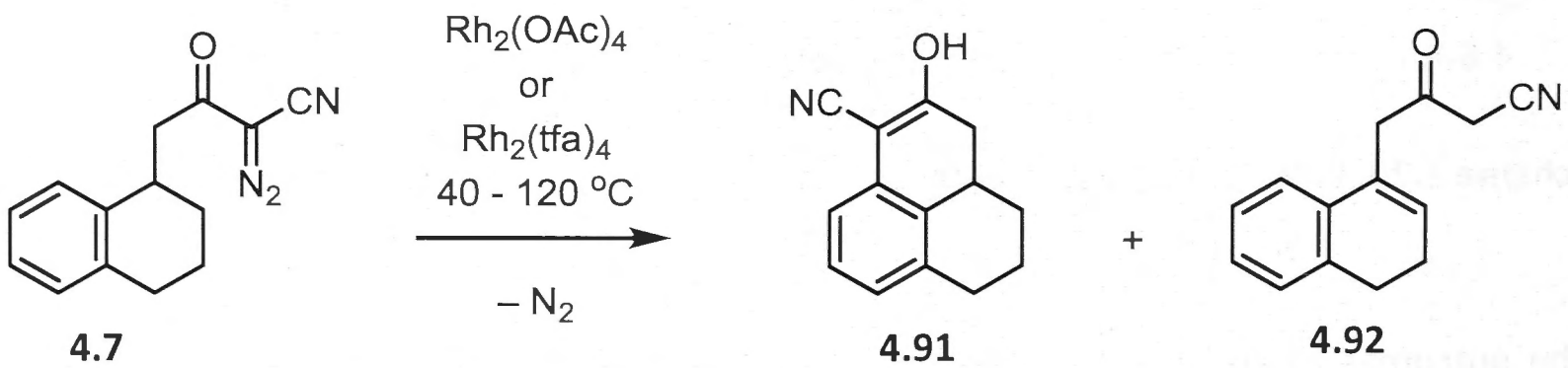
Table 4.5. Products Formed as a Result of the Rh(II)-Catalysed Decomposition of Diazo-β-keto-nitrile **4.6**.

Temperature	$Rh_2(OAc)_4$	$Rh_2(tfa)_4$
40-50 °C	**4.82** (quant.)[a]	**4.86**[c] (91%)[e]
80 °C	**4.82,** trace of **4.84**[b] *Slow addition*: **4.82** (85%)[e]	**4.86**[b, c]
120 °C	**4.82** (quant.)[a]	**4.86**, **4.82** (2:1 ratio by NMR)[d]

[a] Yield by NMR; [b] Complete consumption of the starting material was observed by TLC. This reaction was used for qualitative analysis; [c] A trace of enol **4.82** is visible in the ^{1}H NMR spectrum of the crude material; [d] Ratios were calculated from the ^{1}H NMR spectra of the crude material. [e] Isolated yield.

4.5.2. Reaction of the α-Diazo-β-Ketonitrile 4.7 Derived from 1-Tetralone

When diazoketone **4.7** was subjected to microwave irradiation in the presence of either $Rh_2(OAc)_4$ or $Rh_2(tfa)_4$ then two products were formed. $Rh_2(OAc)_4$-catalysis caused C-H insertion on the aromatic ring to give unstable enol **4.91** (Scheme 4.21), the higher homologue of compound **4.82** arising from the analogous reaction of diazocarbonyl **4.6**. The $Rh_2(tfa)_4$-catalysed reaction gave a mixture of this same enol **4.91** and unstable dihydronaphthalene **4.92**. No evidence for the formation of a Büchner-type product was observed at any stage. The same temperature-dependence of the product distribution observed earlier (see Section 4.5.1.) was also encountered in this case. The results are summarised in Table 4.5.



4.7 **4.91** **4.92**

Yields: See Table 4.21.

Scheme 4.21. Outcomes of the Rh(II)-catalysed decomposition of diazo-β-ketonitrile **4.7**.

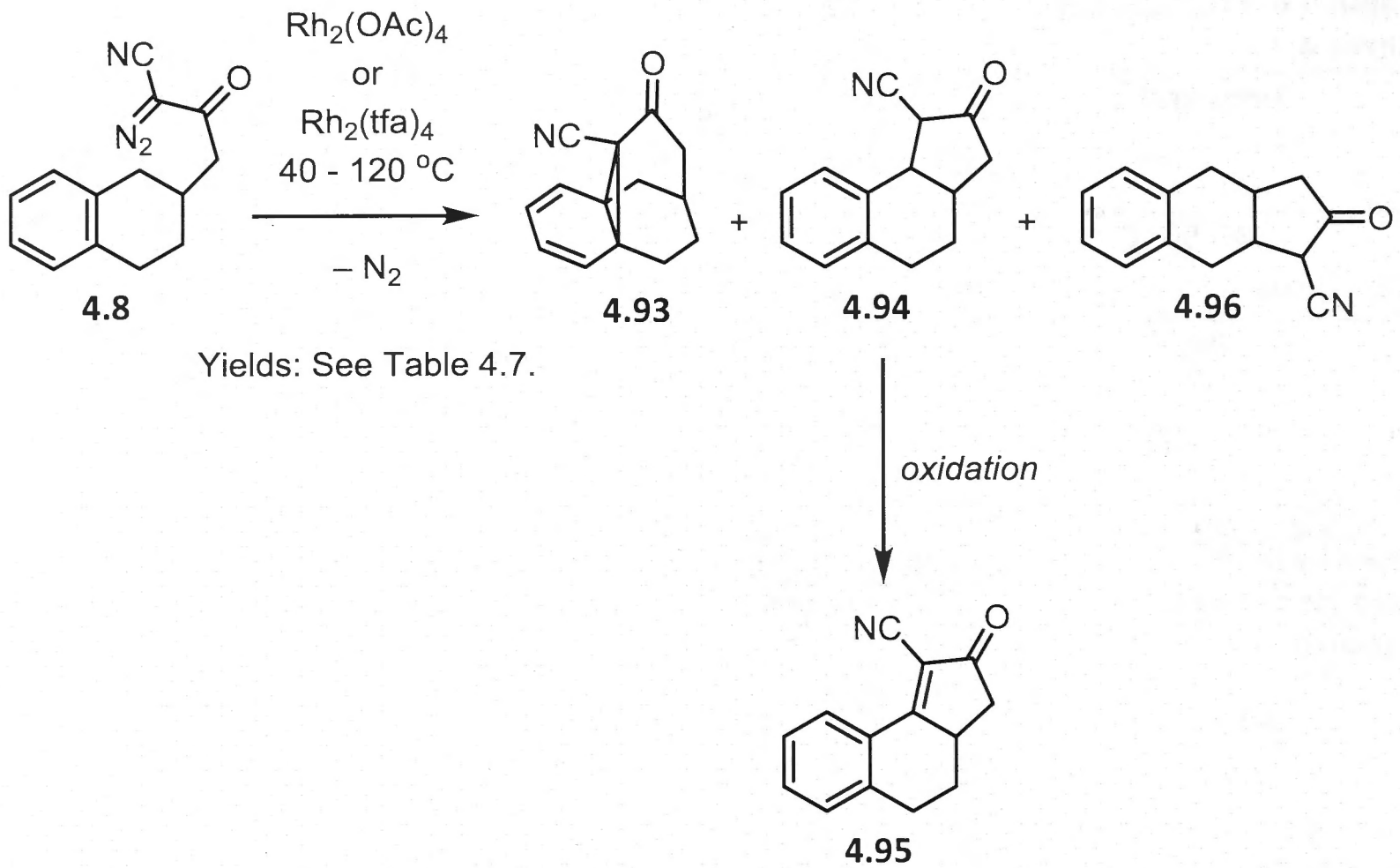
Table 4.6. Products Formed as a Result of the Rh(II)-Catalysed Decomposition of Diazo-β-keto-nitrile **4.7**.

Temperature	$Rh_2(OAc)_4$	$Rh_2(tfa)_4$
40-50 °C	**4.91** (quant.)[a]	**4.91**, **4.92** (1:1 ratio by NMR)[b]
80 °C	*Slow addition*: **4.91** (22%)[c]	**4.91**, **4.92** (1:1 ratio by NMR)[b]
120 °C	decomposition	**4.91**, **4.92** (2:1 ratio by NMR)[b]

[a] Yield by NMR; [b] Complete consumption of the starting material was observed by TLC. This reaction was used for qualitative analysis. Ratios were calculated from the ^{1}H NMR spectra of the crude material. [c] Isolated yield.

4.5.3. Reaction of the α-Diazo-β-Ketonitrile 4.8 Derived from 2-Tetralone

The metal-catalysed decomposition of diazo-β-ketonitrile **4.8** resulted in rather complex reaction mixtures. Even the $Rh_2(OAc)_4$-catalysed process proved to be rather unselective. However, under the various reaction conditions that were explored, one major product (**4.94**, Scheme 4.22) was observed in each instance. This resulted from carbenoid insertion into the adjacent benzylic C-H bond to form a five-membered ring. The structure of this product follows from the single-crystal X-ray analysis of its co-produced dehydro-congener, **4.95**, which is presumed to arise *via* an aerial oxidation process. Small amounts of a product thought to be the aliphatic C-H insertion product **4.96** were observed in some of the crude reaction mixtures. The ^{1}H NMR spectrum of this product showed a single signal due to four aromatic protons (at δ 7.1), suggesting a higher degree of symmetry within the structure. It was thus assumed to be the aliphatic C-H insertion product **4.96**, which is only asymmetric due to the nitrile substituent. The ^{1}H NMR spectra of most crude reaction mixtures included this characteristic signal, however, repeated attempts to isolate pure samples of compound **4.96** failed due to its decomposition during flash column chromatography. Not surprisingly, aromatic C-H insertion products were not observed as these would be too strained. Interestingly, though, small amounts of norcaradiene **4.93** were detected in the reaction mixtures, as judged by the presence of characteristic resonances due to the associated diene moiety in the ^{1}H NMR spectrum of the crude product. Traces of this compound were generated in the presence of both $Rh_2(OAc)_4$ and $Rh_2(tfa)_4$. Employing the slow addition method afforded the benzylic insertion product **4.94** in 50% yield along with an inseparable 1:1 mixture (9%) of propelladiene **4.93** and oxidation product **4.95**. Table 4.7 summarises the outcomes of the series of experiments just described.



Yields: See Table 4.7.

Scheme 4.22. Outcomes of the Rh(II)-catalysed decomposition of diazo-β-ketonitrile **4.8**.

Table 4.7. Products Formed as a Result of the Rh(II)-Catalysed Decomposition of Diazo-β-keto-nitrile **4.8**.

Temperature	$Rh_2(OAc)_4$	$Rh_2(tfa)_4$
40-50 °C	**4.96** (quant.)[a]	**4.96, 4.94** (2:1 ratio by NMR)[b]
80 °C	**4.96, 4.94** (trace: **4.93**)[b] *Slow addition*: **4.94** (50%)[c], **4.93/4.95** (1:1, 9%)[c]	**4.96, 4.94** (1:1 ratio by NMR)[b]
120 °C	**4.94**, **4.96** (trace: **4.93**)[b]	**4.96, 4.94** (1:1 ratio by NMR)[b]

[a] Yield by NMR; [b] Complete consumption of the starting material was observed by TLC. This reaction was used for qualitative analysis. Ratios were calculated from the ^{1}H NMR spectra of the crude material. [c] Isolated yield.

Analyses of the ^{1}H NMR spectra of the crude reaction product suggested that the highest yield of Büchner product was obtained during the $Rh_2(OAc)_4$-catalysed decomposition reaction conducted at 100 °C under microwave irradiation conditions. Even then only traces of this material were obtained. Purification of norcaradiene **4.93** proved difficult, with aromatic byproducts persisting even after extensive chromatography. Figure 4.2 depicts the ^{1}H NMR spectrum of compound **4.93** with the resonances due to each proton of the diene moiety clearly apparent due to the asymmetric nature of this propelladiene.

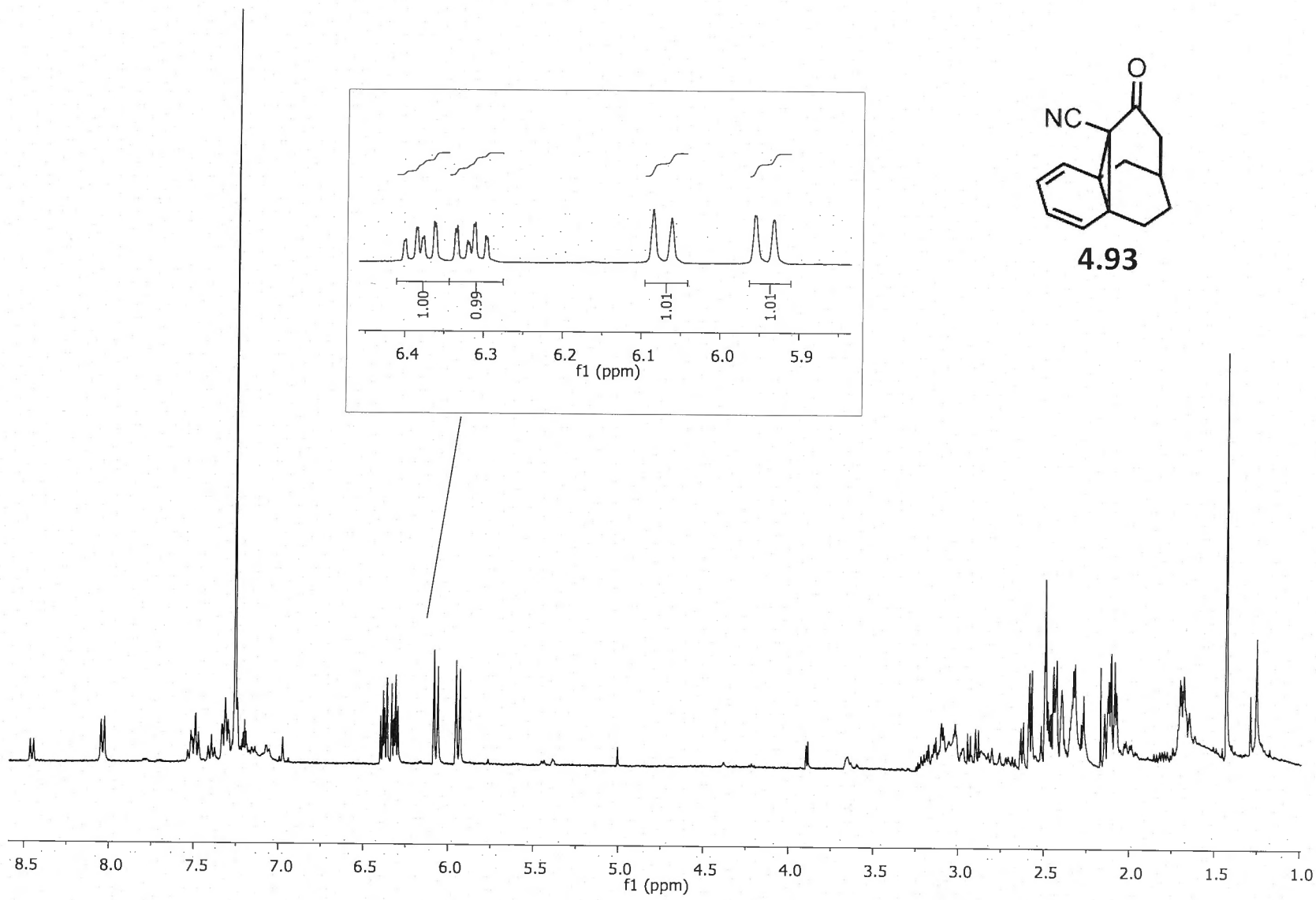
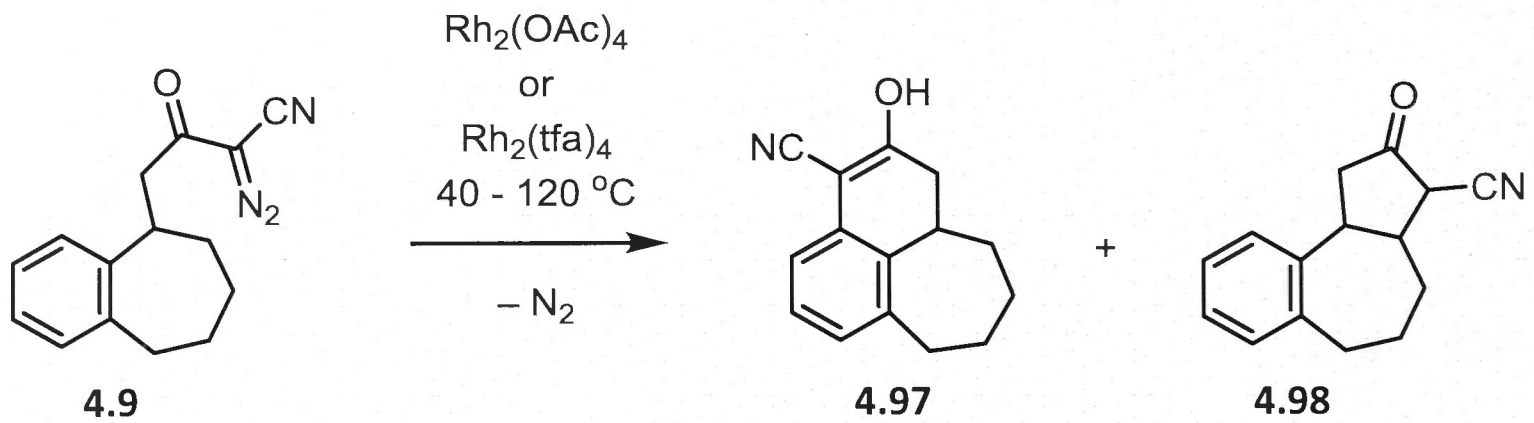


Figure 4.2. 400 MHz ^{1}H NMR spectrum of norcaradiene **4.93** (recorded in $CDCl_3$, additional signals are due to products arising from C-H insertion processes).

As noted earlier, while C-H insertion into five-membered rings gives rise to *cis*-fused bicyclic products, C-H insertion into six-membered rings can result in both *cis*- and *trans*-fused bicyclic ring systems, with the *trans*-product normally being favoured.[3a] The three aliphatic methine signals observed in the ^{1}H NMR spectrum of compound **4.94** display vicinal couplings of 11.3 and 6.1 Hz, the latter being associated with the ring-junction hydrogens. This value speaks in favour of eclipsed protons and thus a *cis*-fused bicyclic ring system. While it is likely to be analogous to that of compound **4.94**, the stereochemistry of fused tricycle **4.96** could not be determined as the relevant signals in the ^{1}H NMR spectrum were obscured.

4.5.4. Reaction of the α-Diazo-β-ketonitrile 4.9 Derived from 1-Benzosuberone

In keeping with the behaviour of congeners **4.6** and **4.7**, the $Rh_2(OAc)_4$-catalysed decomposition of diazo-compound **4.9** yielded product **4.97** (54%, slow addition method) arising from an aromatic C-H insertion process. The reaction catalysed by $Rh_2(tfa)_4$ gave a mixture of this product (**4.97**) and the homobenzylic C-H insertion product **4.98** which was obtained as a single diastereomer (Scheme 4.23). Table 4.7 summarises the results of this series of experiments.



4.9 **4.97** **4.98**

Slow addition: 54%

Scheme 4.23. Outcomes of the Rh(II)-catalysed decomposition of diazo-β-ketonitrile **4.9**.

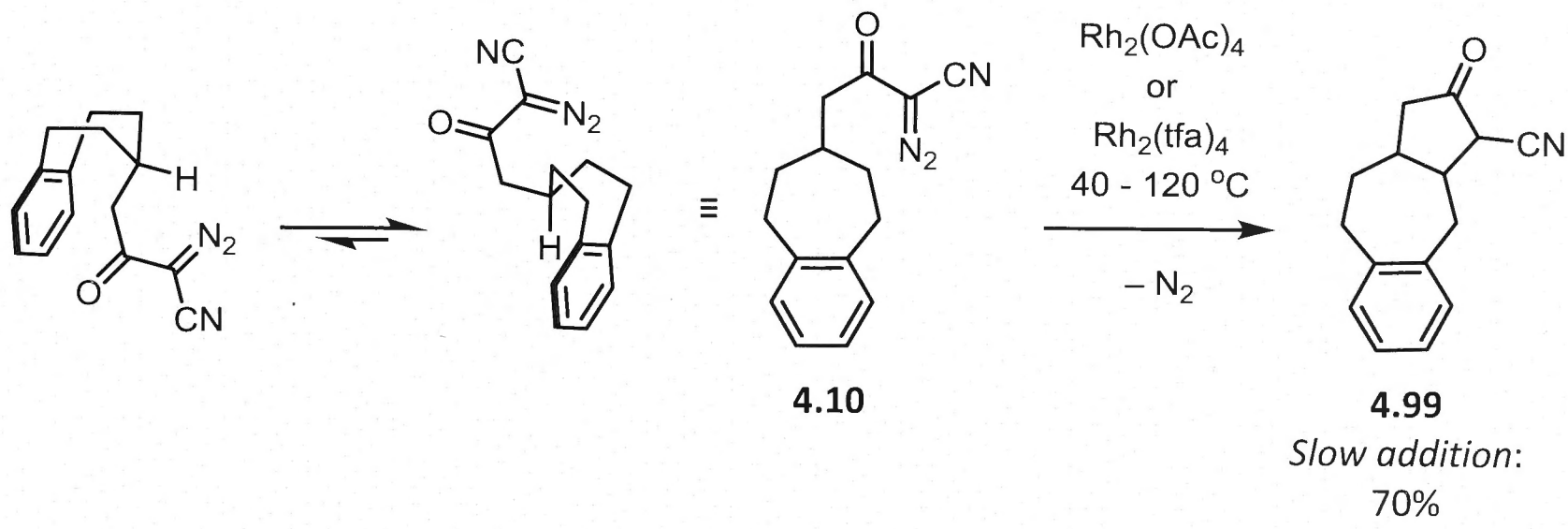
Table 4.8. Products Formed as a Result of the Rh(II)-Catalysed Decomposition of Diazo-β-keto-nitrile **4.9**.

Temperature	$Rh_2(OAc)_4$	$Rh_2(tfa)_4$
40-50 °C	**4.97** (quant.)[a]	**4.97**, **4.98** (1:1 ratio by NMR)[b, c]
80 °C	**4.97** (quant.)[a] *Slow addition*: **4.97** (54%)[d]	**4.97** (55%)[d], **4.98** (24%)[d] (1:1 ratio by NMR)[c]
120 °C	**4.97** (quant.)[a]	**4.97**, **4.98** (1:1 ratio by NMR)[b, c]

[a] Yield by NMR; [b] Complete consumption of the starting material was observed by TLC. This reaction was used for qualitative analysis. [c] Ratios were calculated from the ^{1}H NMR spectra of the crude material; [d] isolated yield.

4.5.5. Reaction of the α-Diazo-β-ketonitrile 4.10 Derived from 3-Benzosuberone

Diazocarbonyl **4.10** was unique amongst the series of diazo-β-ketonitriles studied here in that the same product, **4.99**, was obtained regardless of the catalyst or reaction temperature used. No trace of the hoped-for Büchner product was found in any of the reaction mixtures. Using the slow addition protocol compound **4.99** was obtained in 70% yield. While substrate **4.10** is symmetrical and thus seems perfectly aligned (see tub-like conformation shown in Scheme 4.24) to engage in a Büchner reaction, the seven-membered ring causes the tether to be 'floppy' and thus not direct the diazo-moiety to come into close enough proximity to the aromatic ring. Accordingly, C-H insertion into the aliphatic γ-methylene groups is much more competitive as a result.



4.10

4.99
Slow addition:
70%

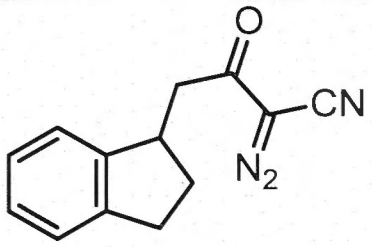
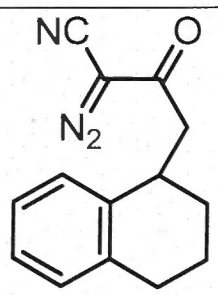
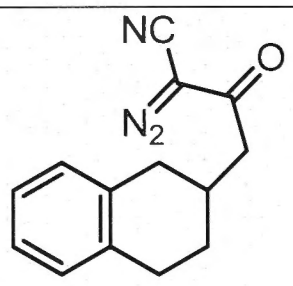
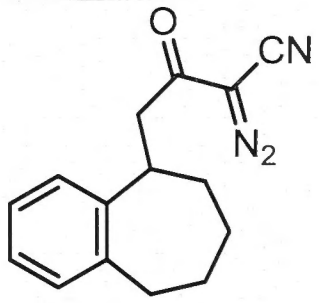
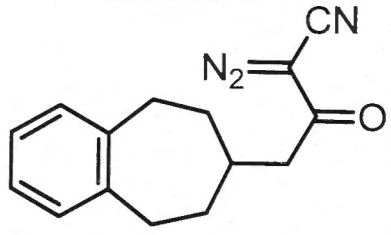
Scheme 4.24. Outcome of the Rh(II)-catalysed decomposition of diazo-β-ketonitrile **4.10.**

The stereochemical outcome of C-H insertion into seven-membered rings has not been reported in the literature. Unfortunately, the ^{1}H NMR spectra of compounds **4.98** and **4.99** were complex and various relevant signals partly obscured. As a result, the stereochemistry could not be determined. However, given the single set of signals appearing in the ^{13}C NMR spectrum of this material it was apparent that formation of just one diastereomer had occurred in both cases. As discussed above (Section 4.3.5), studies by Taber *et al.*[3a] showed that the *trans*-configuration is favoured for C-H insertion processes into six-membered rings and into *n*-alkyl chains leading to the formation of five-membered rings. Thus, it is proposed that in the case of benzosuberone derivatives **4.98** and **4.99** the two alkyl rings are fused to one another in a *trans*-manner.

4.6. Conclusion

Various reaction conditions were tested in attempts to engage substrates **4.6** - **4.10** in Büchner reactions. Such a reaction only occurred in two instances (see Sections 4.5.1 and 4.5.3, and Table 4.9, entries 1 and 3) and just a trace of the hoped-for propellane-type product was observed in one case (see Section 4.5.3, and Table 4.8, entry 3).

Table 4.9. Summary of the Outcomes of the $Rh_2(OAc)_4$- and $Rh_2(tfa)_4$-Catalysed Decomposition of Diazo-β-ketonitriles **4.6** - **4.10**.

Entry	Diazo-compound	$Rh_2(OAc)_4$-Catalysed Decomposition[a]	$Rh_2(tfa)_4$-Catalysed Decomposition[a]
1	 (**4.6**)	Aromatic C-H insertion Büchner reaction[b]	Hydride shift Aromatic C-H insertion
2	 (**4.7**)	Aromatic C-H insertion	Hydride shift Aromatic C-H insertion
3	 (**4.8**)	Aliphatic C-H insertion Büchner reaction[b]	Aliphatic C-H insertion Büchner reaction[b]
4	 (**4.9**)	Aromatic C-H insertion	Aliphatic C-H insertion Aromatic C-H insertion
5	 (**4.10**)	Aliphatic C-H insertion	Aliphatic C-H insertion

[a] Listed in order of decreasing yield for each substrate; [b] Traces of the product resulting from a Büchner reaction were present in the crude material as judged by the ^{1}H NMR spectra.

The diazo-β-ketonitriles that were tethered to the benzylic position (as seen in substrates **4.6**, **4.7** and **4.9**) favoured aromatic over aliphatic C-H insertion, whereas diazo-compounds **4.8** (containing a homobenzylic tether) and **4.10** (containing an aliphatic tether) underwent C-H

insertion into methylene groups. This suggests that in the presence of $Rh_2(OAc)_4$ aromatic C-H insertion is favoured over aliphatic C-H insertion. When C-H insertion into methylene groups did occur, it did not show any selectivity for the aliphatic over the benzylic position. This was unexpected as the benzylic position is generally deactivated when the aromatic ring is unsubstituted.

The $Rh_2(tfa)_4$-catalysed decomposition of diazocarbonyls **4.6** and **4.7** (containing benzylic tethers) resulted in a hydride shift to give the 1*H*-indene and 1,2-dihydronaphthalene derivatives (**4.86** and **4.92**, respectively). Similar reactions with diazocarbonyls have been reported previously[21,31-32] albeit only in the presence of adjacent (and stabilising) heteroatoms. Interestingly, diazo-compound **4.9** derived from 1-benzosuberone only engaged in a single type of C-H insertion reaction under the abovementioned reaction conditions and no product resulting from an "anomalous C-H insertion" reaction was observed. This may be due to C-C double bonds being less stable in seven-membered rings.[§]

While the abovementioned results have inherent interest, they show that the route used in effecting the synthesis of propellane **2.37** cannot be extended to any analogues at all and is therefore not suitable for the synthesis of fenestranes of the general form **4.16** - **4.20**. In essence, competing C-H insertion reactions have thwarted all efforts to carry out the desired chemistry as proposed in Section 4.1.

[§] The HWE reaction of 1-benzosuberone (**4.4**) also resulted in formation of the *E*- and *Z*-diastereomers. No isomerisation to form a product containing an endocyclic C-C double bond was observed.

4.7. References

(1) Morris, J. C.; Mander, L. N.; Hockless, D. C. R. *Synthesis* **1998**, *S1* 455.

(2) Frey, B.; Wells, A. P.; Roden, F.; Au, T. D.; Hockless, D. C.; Willis, A. C.; Mander, L. N. *Aust. J. Chem.* **2000**, *53*, 819.

(3) a) Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 7686; b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669; c) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1047.

(4) Duddeck, H.; Kennedy, M.; McKervey, M. A.; Twohig, F. M. *J. Chem. Soc., Chem. Commun.* **1988**, 1586.

(5) a) Doyle, M. P.; Protopopova, M. N.; Peterson, C. S.; Vitale, J. P.; McKervey, M. A.; García, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 7865; b) Ye, T.; Garcia, C. F.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1373; c) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296.

(6) a) Maguire, A. R.; O'Leary, P.; Harrington, F.; Lawrence, S. E.; Blake, A. J. *J. Org. Chem.* **2001**, *66*, 7166; b) Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7304.

(7) Cordi, A. A.; Lacoste, J.-M.; Hennig, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3.

(8) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

(9) Kulkowit, S.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1981**, 616.

(10) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

(11) Personal discussion with Prof. Lew Mander.

(12) a) R. Maguire, A.; Rachael Buckley, N.; O'Leary, P.; Ferguson, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, *0*, 4077; b) Levin, S.; Nani, R. R.; Reisman, S. E. *Org. Lett.* **2010**, *12*, 780.

(13) Buttle, L. A.; Morris, J. C.; Mander, L. N. *Arkivoc* **2003**, 118.

(14) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(15) a) Kirmse, W.; Schladetsch, H. J.; Bücking, H.-W. *Chem. Ber.* **1966**, *99*, 2579; b) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.

(16) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1991**, *56*, 7065.

(17) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.

(18) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547.

(19) Watanabe, N.; Ohtake, Y.; Hashimoto, S.-i.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1995**, *36*, 1491.

(20) Stork, G.; Kazuhiko, N. *Tetrahedron Lett.* **1988**, *29*, 2283.

(21) Clark, J. S.; Dossetter, A. G.; Russell, C. A.; Whittingham, W. G. *J. Org. Chem.* **1997**, *62*, 4910.

(22) Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749.

(23) Rogers, D. H.; Frey, B.; Roden, F. S.; Russkamp, F.-W.; Willis, A. C.; Mander, L. N. *Aust. J. Chem.* **1999**, *52*, 1093.

(24) a) Maguire, A. R.; Buckley, N. R.; O'Leary, P.; Ferguson, G. *Chem. Commun. (Cambridge, U. K.)* **1996**, 2595; b) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774.

(25) Ewing, G. D.; Paquette, L. A. *J. Org. Chem.* **1975**, *40*, 2965.

(26) Van Der Veen, R. H.; Geenevasen, J. A. J.; Cerfontain, H. *Can. J. Chem.* **1984**, *62*, 2202.

(27) a) Ferraz, H. M. C.; Silva Jr, L. F. *Tetrahedron* **2001**, *57*, 9939; b) Kukovinets, O. S.; Kislitsyn, M. I.; Zainullin, R. A.; Mukhamedzyanova, A. A.; Galin, F. Z.; Abdullin, M. I. *Russ. J. Org. Chem.* **2008**, *44*, 362; c) Stroba, A.; Schaeffer, F.; Hindie, V.; Lopez-Garcia, L.; Adrian, I.; Fröhner, W.; Hartmann, R. W.; Biondi, R. M.; Engel, M. *J. Med. Chem.* **2009**, *52*, 4683.

(28) Hellwinkel, D.; Kosack, T. *Liebigs Ann. Chem.* **1985**, *1985*, 226.

(29) a) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797; b) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2011**, *13*, 2514.

(30) Doyle, M. P.; Dyatkin, A. B.; Autry, C. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, *0*, 619.

(31) Mander, L. N.; Owen, D. J. *Tetrahedron Lett.* **1996**, *37*, 723.

(32) a) White, J. D.; Hrnciar, P. *J. Org. Chem.* **1999**, *64*, 7271; b) Clark, J. S.; Wong, Y.-S.; Townsend, R. J. *Tetrahedron Lett.* **2001**, *42*, 6187; c) Clark, J. S.; Dossetter, A. G.; Wong, Y.-S.; Townsend, R. J.; Whittingham, W. G.; Russell, C. A. *J. Org. Chem.* **2004**, *69*, 3886.

Chapter 5

Desymmetrisation of the Caged Core Lactone 1.13

5.1. Desymmetrisation Methods

With the synthesis and biological testing (Chapter 2) of the *meso*-caged core lactone **1.13** completed, the next phase of the present study focused on elaborating the associated diene moiety so as to complete the synthesis of salvileucalin B (**1.3**) itself (Figure 5.1). In their preliminary form, the necessary desymmetrisation studies would be carried out in a non-enantioselective manner simply to establish that the basic chemistry was serviceable. Several options were considered as detailed below.

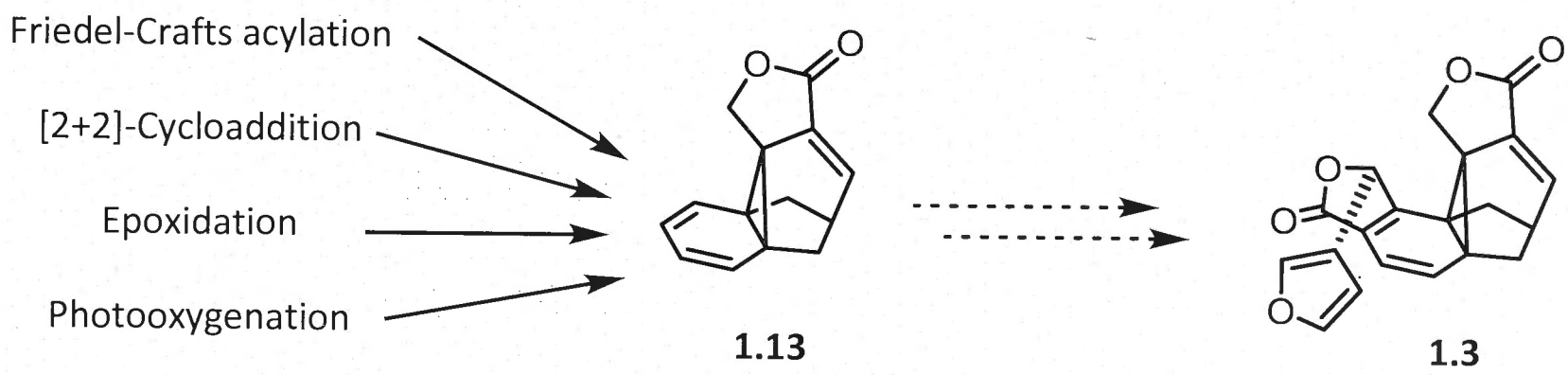


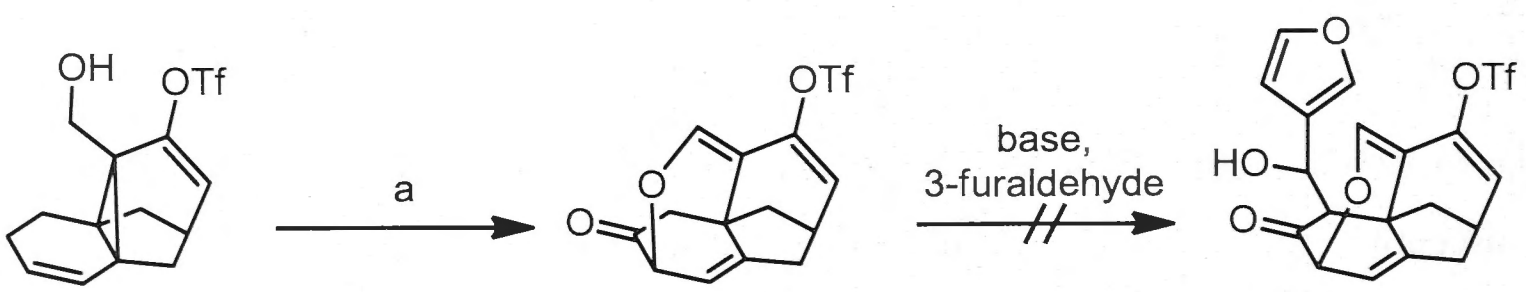
Figure 5.1. Diene functionalisation protocols considered for the purposes of elaborating compound **1.13** to target **1.3**.

It was expected that the diene moiety within compound **1.13** would be electron-rich enough to be susceptible to Friedel-Crafts acylation chemistry by, for example, using furan-3-carboxylic acid chloride in the presence of a Lewis acid as a means for generating the relevant electrophile. In this way, the furan ring associated with the final target would be installed immediately and the remaining carbonyl moiety then introduced so as to establish the second lactone ring. However, when compound **1.13** was subjected to the relevant conditions it failed to react.

Despite the obvious concerns about diastereoselectivity, [2+2]-cycloaddition processes were studied next. In the event, subjection of compound **1.13** to reaction with any one of the ketenes[1] generated from chloro-, dichloro- or trichloro-acetyl chloride in the presence of either finely divided and activated zinc dust or triethylamine proved unsuccessful. Flash vacuum pyrolytic decomposition of Meldrum's acid[2] at 550 °C was also explored as a means of generating the parent ketene. However, all such efforts were unsuccessful with the starting diene being recovered to varying extents in each instance.

5.1.1. Aldol Condensation

As a result of investigations into the mechanism of the [3,5]-sigmatropic rearrangement reaction detailed in Chapter 3 it was established that the aldehyde derived from oxidation of alcohol **4.61** undergoes a [3,3]-sigmatropic rearrangement to give the fenestrane (±)-**4.64** (Scheme 5.1). Accordingly, it was envisaged that compound (±)-**4.64** could be engaged in an aldol condensation reaction with 3-furaldehyde so as to form compound (±)-**5.1** which embodies a furan ring as required in the final target. Indeed, it was thought such a system could be elaborated to the target natural product **1.3** in a total of 14 steps. This would include converting the ketone within compound (±)-**5.1** into the corresponding enol triflate, reducing the masked aldehyde [assuming there is a dynamic equilibrium between fenestrane (±)-**5.1** and the corresponding propellane] followed by a double carbonylative coupling to form both lactone rings in one step. Ultimately, an enantioselective variant of this sequence could be achieved by effecting the enantioselective hydrogenation of alcohol **2.63** and so affording its dihydroanalogue **4.61** in homochiral form. Unfortunately, however, all attempts to effect an aldol condensation reaction between compound (±)-**4.64** and 3-furaldehyde failed, presumably due to the unfavourable kinetics of this process.

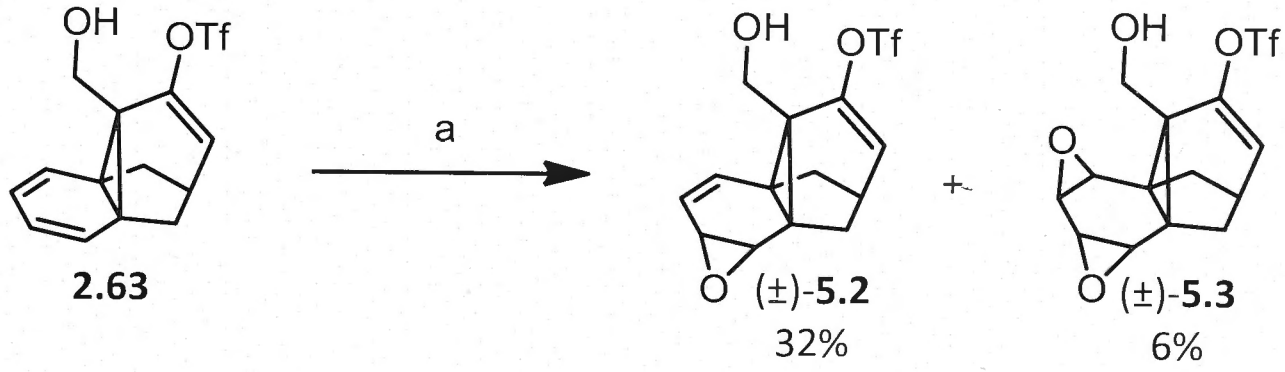


(±)-**4.61** (±)-**4.64** (±)-**5.1**

Scheme 5.1. *Reagents and Condition*: (a) PCC, DCM, rt, 12 h.

5.1.2. Epoxidation

Lactone **1.13** proved to be very susceptible to epoxidation, to the extent that this process was unselective and resulted in a mixture of various mono and more highly oxygenated products. While lowering the reaction temperature to 0 °C slowed the reaction, there was no attendant increase in selectivity. The lactone moiety associated with compound **1.13** did not offer any directing effect for the oxidising agent, presumably because it is too far removed from the diene. In addition, epoxidation of the C-C double bond of the α-methylene-γ-butyrolactone moiety occurred in most cases as evidenced by the absence of a low-field doublet (due to the H-atom of the α,β-unsaturated carbonyl moiety within the precursor) in the ^{1}H NMR spectrum of the crude reaction mixture. These problems were remedied by subjecting the precursor alcohol **2.63** to epoxidation instead (Scheme 5.2). Thus, when compound **2.63** was treated with *m*-CPBA at room temperature for 21 h then the monoepoxide (±)-**5.2** was obtained in 32% yield. Small amounts (6%) of the bisepoxide (±)-**5.3** were also isolated, but a trisepoxide was not observed, presumably because the C-C double bond of the enol triflate moiety was too electron-deficient to react with the electrophilic epoxidising reagent *m*-CPBA.



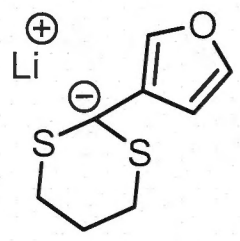
2.63 (±)-**5.2** 32% (±)-**5.3** 6%

Scheme 5.2. *Reagents and Conditions*: (a) *m*-CPBA, DCM, rt, 21 h.

As evidenced by the appearance of a single set of olefinic resonances at δ 6.59 (d) and 5.90 (dd) in its ^{1}H NMR spectrum, it was clear that the monoepoxide (±)-**5.2** had been obtained in diastereomerically pure form. It was expected that the epoxidation process leading to this product had occurred from the α-face of the diene moiety because of the steric hindrance exerted by the molecular substructure carrying the hydroxymethyl group. Curiously, however, spontaneous intramolecular nucleophilic ring-opening of the epoxide by this seemingly perfectly poised hydroxymethyl group was not observed. The bisepoxide (±)-**5.3** displayed four resonances due to epoxide carbons in the ^{13}C NMR spectrum and thus implying that the two epoxide oxygens resided on opposite faces of the associated six-membered ring.

With a sample of epoxide (±)-**5.2** to hand the possibility of obtaining it in an enantioselective manner was pursued. However, employing the Jacobsen[3] protocol for chiral epoxidation[4] did not result in the formation of any product from dienes **2.63** and **1.13**. In contrast, the use of Shi epoxidation conditions[5] gave the desired epoxide **5.2** (48% brsm) after two days. While this reaction was very slow and low yielding, the product displayed a specific rotation of +70 (*c* 0.1, $CDCl_3$) thus suggesting a certain level of asymmetric induction had been achieved.

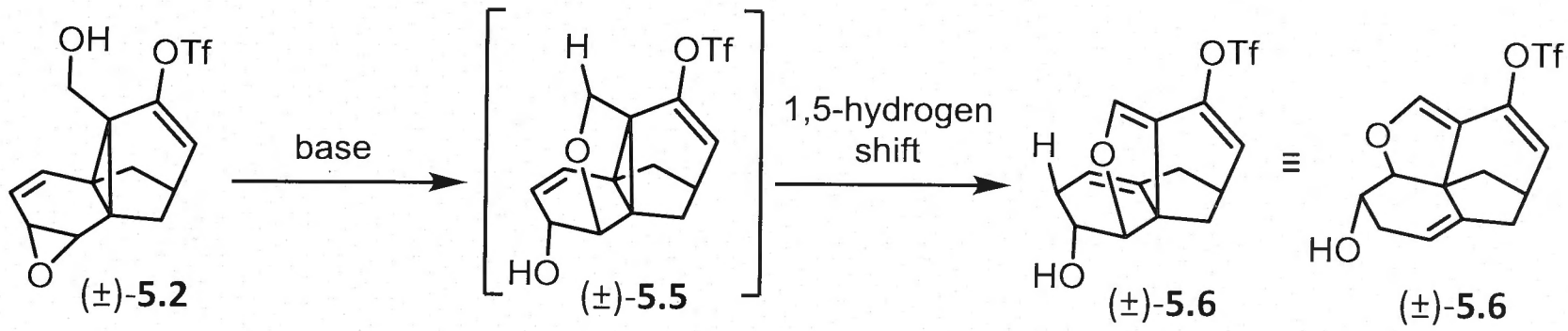
At this stage, efforts to improve the yields of the chiral epoxidation reaction were postponed in favour of exploring relevant epoxide-opening processes. An appropriate nucleophile for the installation of the furan ring was thought to be the lithio-dithiane[6] **5.4** (Figure 5.2) which is accessible from commercially available 3-furaldehyde.



5.4

Figure 5.2. Lithio-dithiane **5.4**, a potential nucleophile for opening epoxide **5.2**.

However, in order to gauge the likely regioselectivity of any epoxide ring-opening process, a reaction was first carried out using the anion derived from deprotonation of dimethyl malonate with LiHMDS. Whilst under such conditions an epoxide-opening reaction did indeed occur, the product isolated was compound (±)-**5.6** - a [5.6.5.6]fenestrane. Clearly, under the reaction conditions used the alcohol moiety within substrate (±)-**5.2** had been deprotonated and the resulting alkoxy anion had then engaged in an internal nucleophilic substitution reaction to give the isomeric system (±)-**5.5** (Scheme 5.3). This was followed by a 1,5-hydrogen shift to give the observed and presumably less strained fenestrane (±)-**5.6** which was obtained in 12 - 20% yield (brsm). In fact, the presence of any trace of base caused this reaction to occur, resulting in formation of compound (±)-**5.6** as the sole observable product of reaction. The observation that base was necessary to initiate this reaction supports the suggested order of events. COSY, HSQC and HMBC NMR experiments were used to confirm the illustrated structure. Furthermore, as with all other fenestranes (Chapter 3), the ^{1}H NMR spectrum of compound (±)-**5.6** displayed the characteristic singlet (at δ 6.48) arising from the proton attached to the cyclic enol-ether residue.



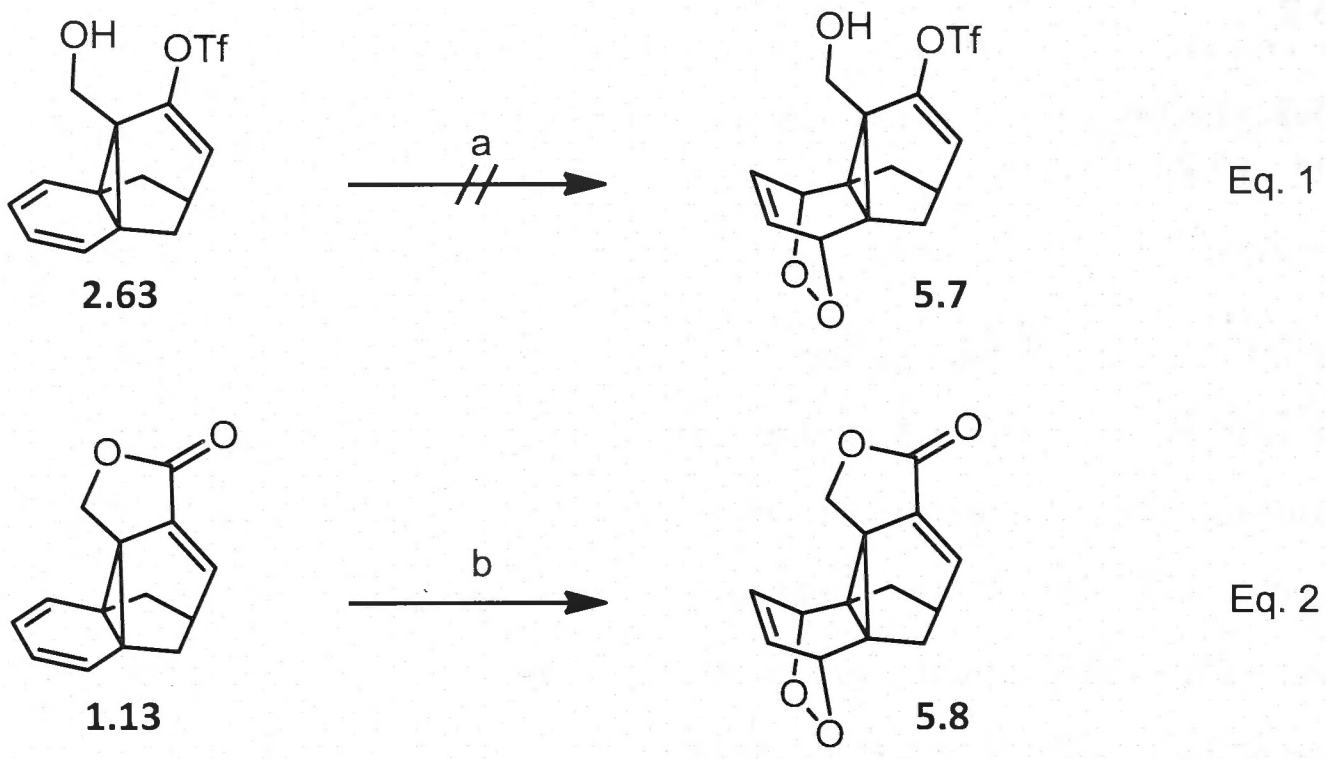
Scheme 5.3. The likely reaction pathway associated with the base-promoted isomerisation of compound (±)-**5.2** to (±)-**5.6.**

While the intervention of the reaction mentioned immediately above thwarted attempts to develop a synthesis of target **1.3** by the pathway mentioned earlier, it served to confirm the stereochemistry originally assigned to monoepoxide (±)-**5.2**. Specifically, then, this internal nucleophilic substitution reaction could only occur if the epoxide was in an *anti*-relationship with respect to the hydroxymethyl group. As such, the original epoxidation reaction must have taken place at the α-face of the diene moiety within the starting diene **2.63**.

5.1.3. Photo-Oxygenation and Kornblum-DeLaMare Rearrangement Reactions as a Means for Functionalising Dienes 1.13 and 2.63

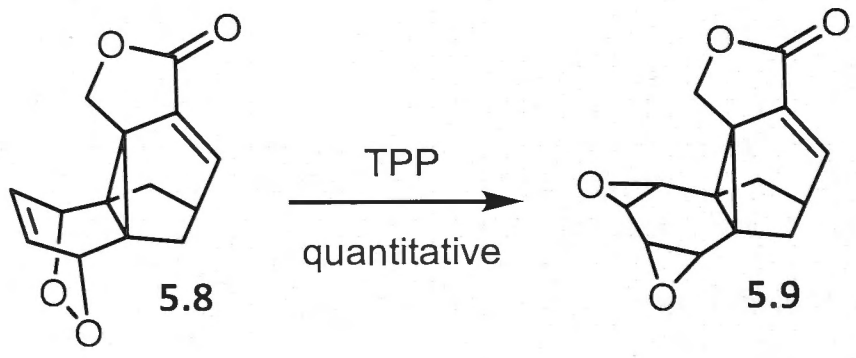
Another possible method for desymmetrising the *meso*-dienes **1.13** and **2.63** would be through addition of singlet oxygen,[7] followed by Kornblum-DeLaMare rearrangement[8] of the initially formed *endo*-peroxide.[9] For the purposes of effecting the first step of this sequence, singlet oxygen was generated *in situ* by bubbling oxygen though a solution containing a photosensitiser - in this case tetraphenylporphyrin (TPP) - that was simultaneously irradiated with high intensity white light produced by a 300 W lamp. The [4+2]-cycloaddition of the thus generated singlet oxygen to the diene moiety of these propelladiene substrates would necessarily give a symmetrical *endo*-peroxide. In the event, when alcohol **2.63** was subjected to the just mentioned conditions for 1 h at 0 °C, (Scheme 5.4, Eq. 1) then a product lacking the symmetry of the starting material was obtained. Thus, in a similar manner to the epoxide opening of compound (±)-**5.2** it is suggested that the alcohol function within compound **5.7** participated in a yet to be identified rearrangement that resulted in cleavage of the initially formed *endo*-peroxide moiety. When the *meso*-lactone **1.13** was subjected to the same conditions, then consumption of the starting material was complete after just 0.17 h and the anticipated *endo*-peroxide **5.8** was obtained as a single diastereomer in 40% yield (Eq. 2). Apparently, then, the steric hindrance exerted by the cyclopropane and lactone moieties within the starting material was sufficient to direct the addition of singlet oxygen to the α-face

of the diene and thus establishing an *anti*-relationship between the peroxidic and lactone moieties within product **5.8**.



Scheme 5.4. *Reagents and Conditions*: (a) O_2 (1 atm), TPP, 300 W white light source, DCM, 0 °C, 1 h; (b) O_2 (1 atm), TPP, 300 W white light source, DCM, 0 °C, 0.17 h.

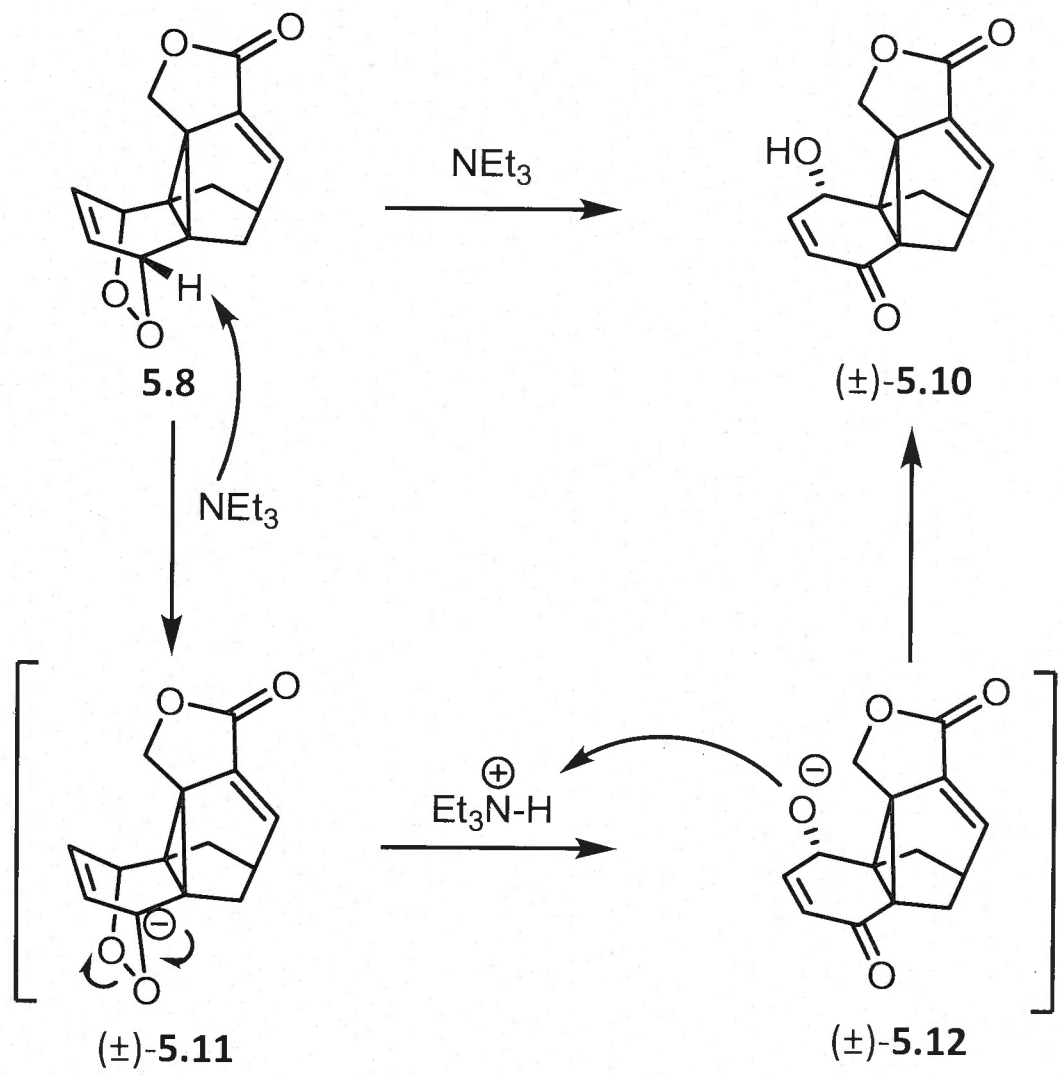
The crystalline *endo*-peroxide **5.8** was purified by flash column chromatography. However, complete removal of contaminating TPP was difficult and the presence of even traces of this material in the primary photoproduct catalysed the rearrangement of the *endo*-peroxide (**5.8**) to the isomeric and still symmetrical bisepoxide[10] **5.9** (Scheme 5.5). This occurred both in solution and in the solid state. If the temperature at which the initial [4+2]-cycloaddition reaction of diene **1.13** with singlet oxygen was allowed to exceed 0 °C then co-formation of the same bisepoxide was observed during the reaction. The use of the lower intensity light (as produced by a common 100 W bulb) increased the reaction time of the [4+2]-photocycloaddition reaction to 1 h as well as increasing the amounts of co-produced bisepoxide **5.9**.



Scheme 5.5. TPP-catalysed decomposition of *endo*-peroxide **5.8** to form the symmetrical bisepoxide **5.9**.

When subjected to reaction with various bases the *endo*-peroxide **5.8** engaged in the anticipated Kornblum-DeLaMare rearrangement (Scheme 5.6). So, for example, in the presence of triethylamine then compound (±)-**5.10** was obtained in 89% yield after 0.33 h at room temperature while co-produced and chromatographically separable bisepoxide **5.9** was obtained in 10% yield. To minimize the time that the *endo*-peroxide **5.8** was exposed to traces of TPP, the crude product of the photo-oxygenation reaction was immediately treated with triethylamine and the resulting solution stirred at room temperature for 0.5 h. By such means the desired γ-hydroxyenone (±)-**5.10** was produced directly and in 92% yield. Bisepoxide **5.9** was also formed in 7% yield. Interestingly, addition of triethylamine at the start of the photo-oxygenation process seemed to inhibit the [4+2]-cycloaddition reaction and so this protocol did not provide a useful means of generating compound (±)-**5.10**.

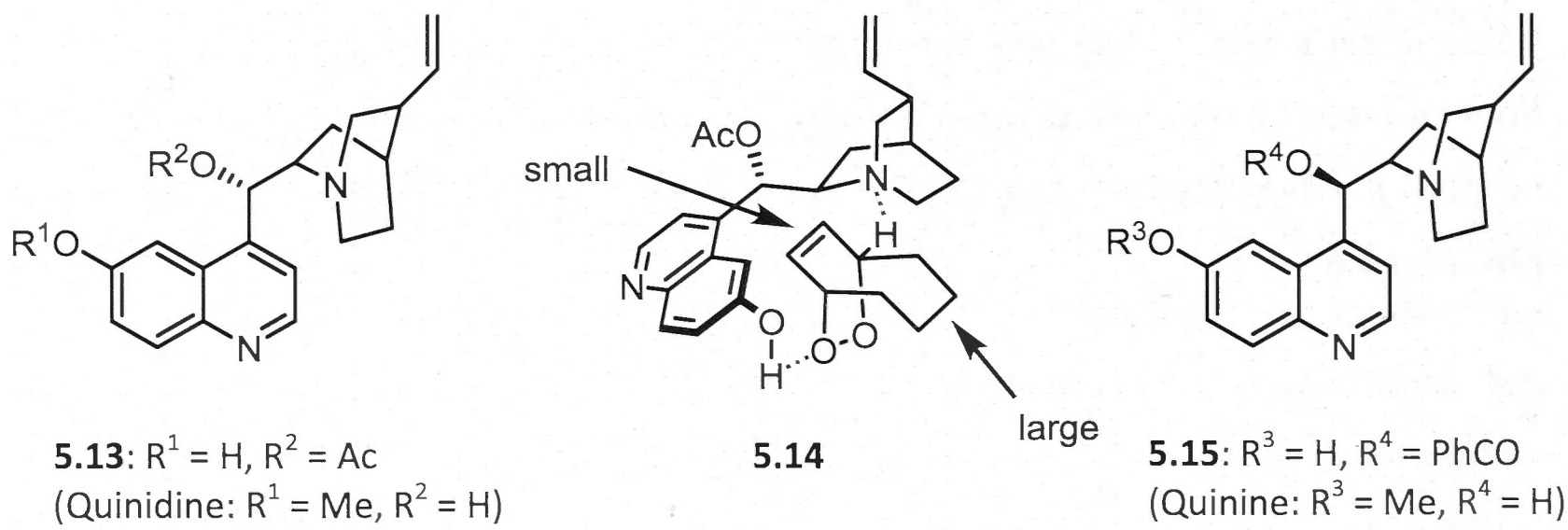
The generally accepted mechanism for the Kornblum-DeLaMare rearrangement is shown in Scheme 5.6.[11] Thus, deprotonation of the oxymethine hydrogen associated with the *endo*-peroxide residue within compound **5.8** is concomitant with rearrangement of the ensuing (or incipient) carbanion (±)-**5.11** and thus forming the more stable alkoxide (±)-**5.12** that results from cleavage of the *endo*-peroxide moiety. Clearly, the stereochemical disposition of the hydroxyl group in product (±)-**5.10** reflects the orientation of the peroxidic oxygens in the precursor **5.8**.



Scheme 5.6. Likely mechanism of the Kornblum-DeLaMare rearrangement of *endo*-peroxide **5.8**.

Compound (±)-**5.10** could be crystallised from deuterated chloroform and thus allowing a single-crystal X-ray analysis of this material to be undertaken. The derived ORTEP is shown in Appendix 10.

In light of these results, the desymmetrisation of *endo*-peroxide **5.8** using a chiral base was explored. Work by Toste *et al.*[8b] showed that in the presence of catalytic amounts of a chiral base such as the quinidine-derived system **5.13** (Figure 5.3) certain simple *endo*-peroxides can be converted into the corresponding γ-hydroxyenones in up to 99% enantiomeric excess. A model to account for the observed enantioselectivity of this process was proposed, as shown for the opening of the cyclo-1,3-octadiene-derived *endo*-peroxide (complex **5.14**). Consistent with such a proposal, when the cyclo-1,3-octadiene-derived *endo*-peroxide was subjected to reaction with the pseudo-enantiomeric quinine-derived base **5.15**, then the enantiomer of the corresponding γ-hydroxyenone was obtained in almost identical ee.



5.13: R^1 = H, R^2 = Ac
(Quinidine: R^1 = Me, R^2 = H)

5.14

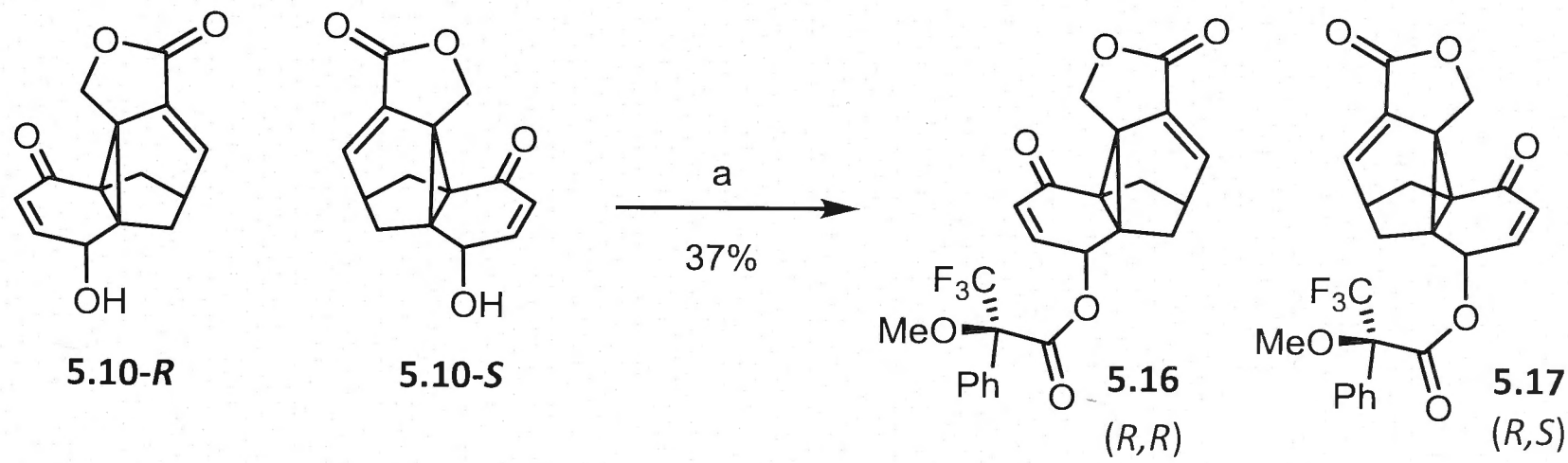
5.15: R^3 = H, R^4 = PhCO
(Quinine: R^3 = Me, R^4 = H)

Figure 5.3. Model for the enantioselective Kornblum-DeLaMare rearrangement of *endo*-peroxides by chiral, cinchona alkaloid-derived bases **5.13** and **5.15**.

Based on these results it was supposed that a similar enantioselectivity could be achieved in the desymmetrisation of *endo*-peroxide **5.8**. However, due to the lack of ready access to quinidine and because it was necessary to test the above-mentioned hypothesis on *endo*-peroxide **5.8** as soon as possible, the chiral catalyst used in this case was the quinine-derived one, *viz*. compound **5.15**[12]. As such, even though the substrate required for the completion of a total synthesis of the target compound **1.3** was compound **5.10-*R***, the **5.10-*S*** enantiomeric form of this γ-hydroxyenone was expected to predominate in the above-mentioned reaction. In the event, exposure of *endo*-peroxide **5.8** to the quinine-derived chiral base **5.15** at room temperature for 48 h gave compound **5.10** in 26% yield. This was accompanied by significant quantities (70%) of the bisepoxide **5.9**. Product **5.10** obtained by such means displayed a specific rotation of +120 (*c* 0.1, $CDCl_3$).

5.1.4. Determination of the Enantiomeric Purity of the γ-Hydroxyenone 5.10 Obtained *via* the Toste-Modification of the Kornblum-DeLaMare Reaction

Efforts to separate the constituent enantiomeric forms of compound (±)-**5.10** using chiral GC techniques were unsuccessful. As such, the Mosher esters[13] of the constituent alcohols were prepared (Scheme 5.7). Specifically, then, alcohol (±)-**5.10** was subjected to reaction with the acid chloride generated from *R*-(+)-MTPA, in the presence of DMAP at 105 °C. After purification using column chromatography on basic alumina, an admixture of the desired and diastereomerically related esters **5.16** and **5.17** was obtained as a clear, colourless oil in 37% combined yield. The low yield was attributed to sensitivity of the products to column chromatographic protocols, even those involving neutral or basic alumina. It was thus deemed more reliable to analyse the NMR spectrum recorded on the crude reaction product in order to determine product ratios more accurately. In the event, both the ^{1}H and ^{19}F NMR spectra of the crude mixture of Mosher esters showed that they had been obtained as a 1:1 mixture.



Scheme 5.7. *Reagents and Conditions*: (a) *R*-(+)-MTPA, 2,4,6-trichlorobenzoyl chloride, NEt_3, THF, rt, 1.5 h, then DMAP, toluene, 105 °C, 1 h.

When the enantioenriched form of compound **5.10** was subjected to the same Mosher ester-forming conditions, column chromatographic purification of this crude material was unsuccessful in that no compound was isolated from any of the fractions. Accordingly, analyses were carried out on the crude esterification mixture which revealed the presence of a 2:1 mixture of the diastereomers as determined by integration of the relevant signals in the ^{1}H and ^{19}F NMR spectra. This product ratio is in accord with the work published by Toste in that when subjecting cyclohexadiene-derived *endo*-peroxides to enantioselective Kornblum-DeLaMare reaction conditions, lower enantiomeric excesses were obtained than when *endo*-peroxides arising from larger rings were involved.

Careful analysis of the ^{1}H NMR spectrum of the crude mixture of Mosher esters derived from the enantioenriched γ-hydroxyenone **5.10**, most particularly considering the differences in

chemical shifts resulting from the anisotropic effect exerted by the phenyl ring associated with the *R*-Mosher ester residues within these substrates, allowed for assignment of the stereochemistry. Figure 5.4 shows those protons (numbered in red) associated with the two diastereomeric forms of these esters that would be expected to experience the greatest shielding effects. The relevant resonances appearing in the ^{1}H NMR spectrum of this mixture and a comparison of the differences in chemical shift are presented in Table 5.1. Comparable analyses of the corresponding ^{13}C NMR spectral data were less fruitful. Thus, a ^{13}C-NMR spectrum could only be obtained on the 1:1 mixture of diastereomers **5.16** and **5.17** arising from the esterification of the racemic form of alcohol **5.10**. Furthermore, even with the aid of two-dimensional NMR experiments few of the observed carbon resonances could be assigned to the individual diastereomers.

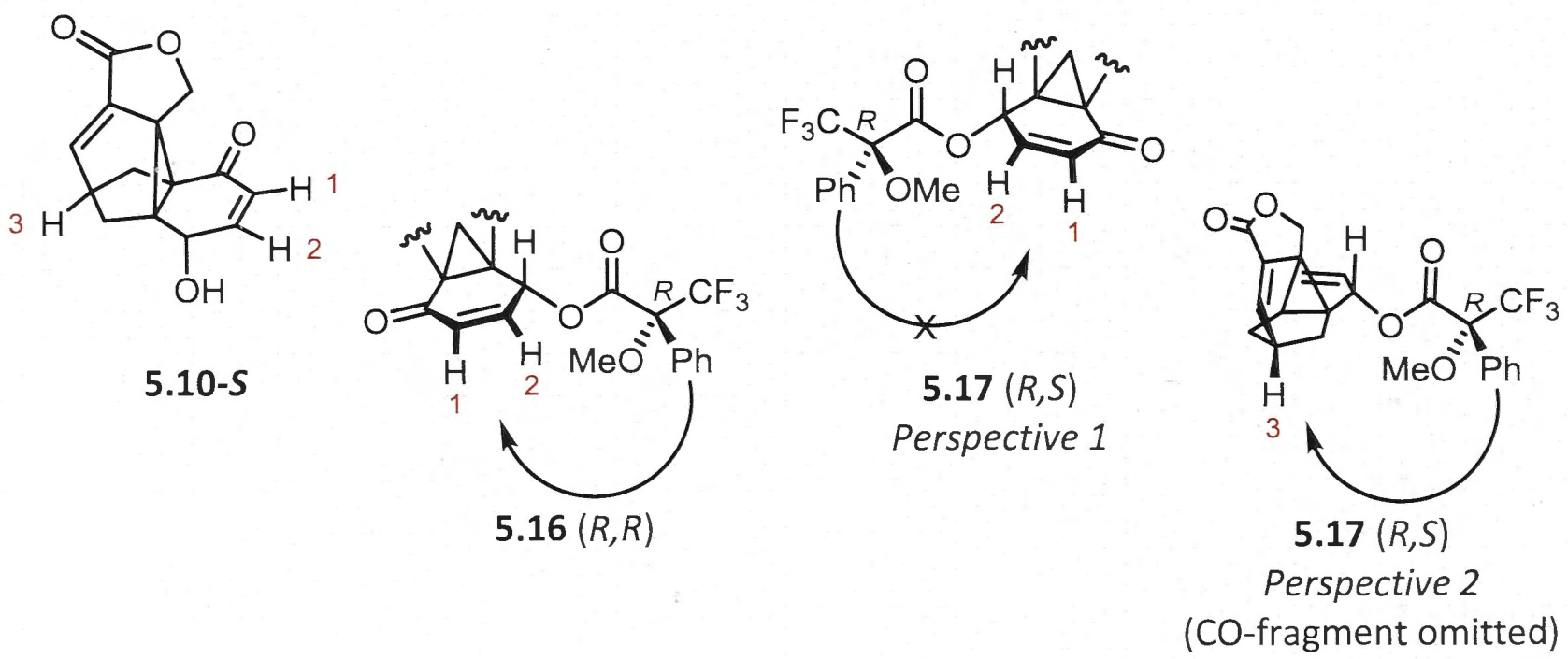


Figure 5.4. Key protons influenced by the anisotropic effect of the phenyl group within Mosher esters **5.16** and **5.17**.

Table 5.1. Comparisons of the ^{1}H and ^{13}C Resonances Observed in the NMR Spectra of Mosher Esters **5.16** and **5.17**.

^{1}H NMR [δ_H]			^{13}C NMR [δ_C]	
Compound **5.16**[a]	Compound **5.17**[a]	Multiplicity, *J* (Hz), Integration	Compounds **5.16** and **5.17**[b,d]	Signal
7.49 - 7.38	7.49 - 7.38	complex m, 2x4H	193.5/193.4	CO
7.26/7.23[c]	7.26/7.23[c]	d, 7.0, 2x1H	167.3	CO
6.78	6.81	dd, 5.0, 10.6, 2x1H	165.9/165.8	CO
6.23	6.28	d, 10.3, 2x1H	138.8/138.7	CH
5.98	6.01	d, 4.8, 2x1H	137.5/137.4	CH
4.37	4.37	q, 9.5, 2x2H	132.9/132.8	CH
3.48/3.54[c]	3.48/3.54[c]	d, 1.1, 2x3H	131.6/131.1	C
3.02	2.93	m, 2x1H	130.1/130.0	CH
1.97	1.97	dd, 5.0, 12.7, 2x1H	128.7	CH
1.89	1.63	dd, 4.8, 12.4, 2x1H	128.6	CH
1.33	1.33	dd, 8.7, 12.4, 2x2H	128.2	C
1.08	0.89	d, 12.4, 2x1H	127.3/127.3	CH
-	-	-	127.0/126.9	CH
-	-	-	124.1/124.0	C
-	-	-	66.7/66.4	CH
-	-	-	66.2	CH_2
-	-	-	55.7/55.4	CH_3
-	-	-	38.5/38.3	C
-	-	-	37.3/37.2	C
-	-	-	35.5/35.4	C
-	-	-	32.1/32.1[e]	CH
-	-	-	28.8/28.3[e]	CH_2
-	-	-	27.0	CH_2

[a] Recorded in $CDCl_3$ at 400 MHz. [b] recorded in $CDCl_3$ at 125 MHz. [c] The resonances were covered or obscured in the corresponding ^{1}H NMR spectrum of the enantioenriched crude product mixture and thus no proof was obtained for their assignment to one diastereomer. [d] These resonances were observed in the ^{13}C NMR spectrum of the racemic mixture of the diastereomerically related compounds **5.16** and **5.17**. [e] This resonance could be assigned to the major diastereomer with the use of a gHSQC NMR experiment.

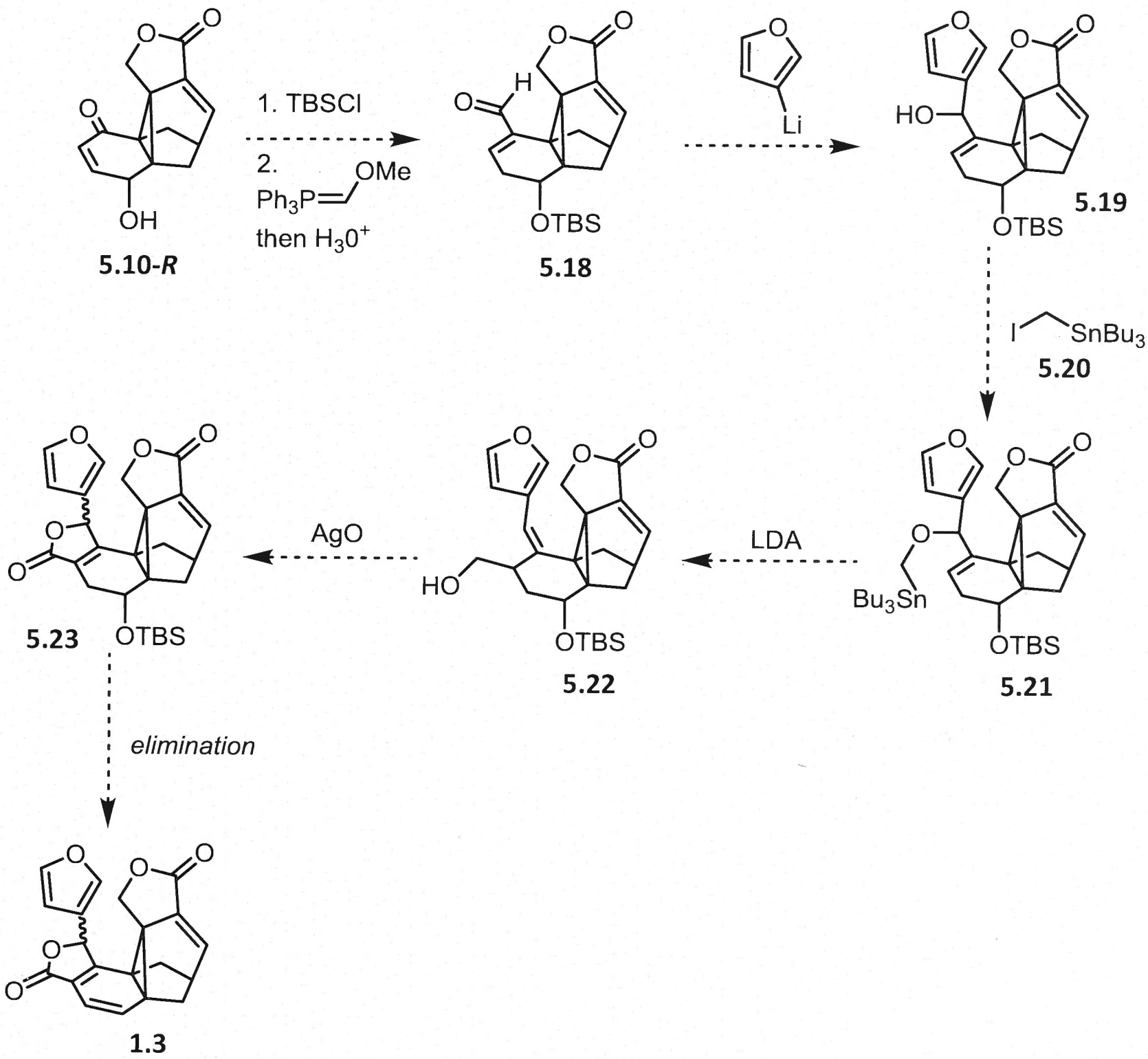
An important clue as to which diastereomer, and thus which enantiomeric form of compound **5.10**, was predominant derived from comparing the resonances observed in the olefinic regions of the ^{1}H NMR spectra of compounds **5.16** and **5.17**. Specifically, the resonances due to

the H1 and H2 of Mosher ester **5.16** (derived from enantiomer **5.10-*R***) were expected to be shifted upfield relative to their counterparts in the other diastereomer due to the preferential shielding effect of the associated phenyl ring in the former compound. Indeed, the resonance due to H1 (at δ 6.23) in compound **5.16** was shifted upfield by 0.05 ppm relative to its counterpart associated with diastereomer **5.17**. Similarly, the resonance due to H2 (appearing at δ 6.78 in the first diastereoisomer) was shifted by 0.03 ppm. As expected, these upfield-shifted signals belonged to the minor product. The characteristic multiplet due to H3 served as another indicator of the predominant stereoisomer. For Mosher ester **5.17** (derived from enantiomer **5.10-*S***) the resonance due to this proton was expected to experience a shielding effect and thus appear at higher field, in this case at δ 2.93. The difference between these signals was 0.09 ppm, a significant shift. The more upfield signal belonged to the major product, consistent with the observations made regarding the olefinic region described above.

From the above observations it was concluded that the major constituent of the mixture of Mosher esters was compound **5.17**, and thus implying that enantiomer **5.10-*S*** was indeed the major product of the Kornblum-DeLaMare rearrangement reaction. This result is consistent with Toste's stereochemical model as shown in Figure 5.3. Once the other enantiomer, **5.10-*R***, has been obtained using the quinidine-derived catalyst in the Kornblum-DeLaMare reaction, this could be used to complete a total synthesis following the synthetic route proposed in the following (final) section.

5.2. Future Work

The synthetic pathway shown in Scheme 5.8 defines a possible means by which compound **5.10-*R*** could be carried through to the target natural product **1.3**. Key aspects of this proposed sequence rely on work reported by Still[14] and Paquette.[15]



Scheme 5.8. Proposed pathway for the completion of the synthesis of salvileucalin B (**1.3**) from compound **5.10-*R***.

Thus, TBS-protection of the alcohol function within compound **5.10-*R*** would be followed by a Wittig olefination reaction using the anion derived from (methoxymethylene)triphenyl-phosphorane. Acid-catalysed hydrolysis of the ensuing methyl vinyl ether should then give aldehyde **5.18**. Treatment of this last compound with 3-lithiofuran could be expected to deliver alcohol **5.19** which, following its subjection to reaction with organostannane **5.20**,[14] would provide tri-*n*-butylstannyl ether **5.21**. Compounds related to **5.21** are known to undergo [2,3]-Wittig-Still rearrangement[16] and so it might be expected, by analogy, that this could be

converted into compound **5.22**. Oxidation of alcohol **5.22** so formed might, based on Paquette's studies, then be expected to deliver lactone **5.23**.[15] Finally, elimination of the elements of TBS-OH from this last compound would yield the target natural product **1.3**. Efforts to implement such a reaction sequence are now underway in the Banwell Group's laboratories.

5.3. References

(1) a) Brady, W. T.; Hieble, J. P. *J. Am. Chem. Soc.* **1972**, *94*, 4278; b) Sünnemann, H. W.; Banwell, M. G.; de Meijere, A. *Chem.--Eur. J.* **2008**, *14*, 7236.

(2) a) Wentrup, C.; Blanch, R.; Briehl, H.; Gross, G. *J. Am. Chem. Soc.* **1988**, *110*, 1874; b) Brown, R. F. C. *Aust. J. Chem.* **2010**, *63*, 1002; c) Monsandl, T.; Macfarlane, G.; Flammang, R.; Wentrup, C. *Aust. J. Chem.* **2010**, *63*, 1076.

(3) a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801; b) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669.

(4) a) Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev.* **2005**, *105*, 1603; b) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.

(5) a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224; b) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551.

(6) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

(7) a) Dechy-Cabaret, O.; Benoit-Vical, F.; Loup, C.; Robert, A.; Gornitzka, H.; Bonhoure, A.; Vial, H.; Magnaval, J.-F.; Séguéla, J.-P.; Meunier, B. *Chem.--Eur. J.* **2004**, *10*, 1625; b) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052.

(8) a) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880; b) Staben, S. T.; Linghu, X.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12658.

(9) For a useful review covering *endo*-peroxides see: Balci, M. *Chem. Rev.* **1981**, *81*, 91.

(10) a) Boyd, J. D.; Foote, C. S.; Imagawa, D. K. *J. Am. Chem. Soc.* **1980**, *102*, 3641; b) Baran, A.; Çambul, S.; Nebioglu, M.; Balci, M. *J. Org. Chem.* **2012**, *77*, 5086.

(11) Kelly, D. R.; Bansal, H.; Morgan, J. J. G. *Tetrahedron Lett.* **2002**, *43*, 9331.

(12) Shi, M.; Lei, Z.-Y.; Zhao, M.-X.; Shi, J.-W. *Tetrahedron Lett.* **2007**, *48*, 5743.

(13) a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543; b) Gao, N.; Ma, X.; Petit, L.; Schwartz, B. D.; Banwell, M. G.; Willis, A. C.; Cade, I. A.; Rae, A. D. *Aust. J. Chem.* **2013**, *66*, 30.

(14) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(15) Paquette, L. A.; Fristad, W. E. *Heterocycles* **1990**, *31*, 2219

(16) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.

Chapter 6

Experimental Procedures Associated with the Work Reported in Chapters 2 to 5

6.1. General Experimental

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature on a Varian Mercury instrument operating at 300 MHz for proton or 75 MHz for carbon nuclei, or a Varian machine operating at 400 MHz for proton or 100 MHz for carbon nuclei. In certain cases a Varian Inova 500 spectrometer operating at 500 MHz for proton or 125 MHz for carbon nuclei was used. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant *J* (Hz), relative integral] where multiplicity is defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations of the above. The residual $CHCl_3$ peak (δ 7.26) was used as the reference for ^{1}H NMR spectra. The central peak (δ 77.0) of the $CDCl_3$ "triplet" was used as reference for proton-decoupled ^{13}C NMR spectra. The data for ^{13}C NMR spectra are given as chemical shift values (δ). The assignment of the signals observed in various NMR spectra were sometimes assisted by conducting Attached Proton Test (APT), and/or gradient homonuclear ($^{1}H/^{1}H$) correlation spectroscopy (gCOSY), and/or gradient Heteronuclear ($^{1}H/^{13}C$) Single Quantum Coherence (gHSQC) experiments.

Infrared spectra (ν_{max}) were normally recorded on a Perkin-Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin films on KBr plates.

A VG Fisons AutoSpec mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray ionisation (ESI) mass spectra were obtained on a VG Quattro II triple-quadrupole MS instrument operating in positive ionisation mode.

Optical rotations (α) were measured at room temperature using a Perkin-Elmer 241 polarimeter at the sodium-D line (589 nm) and the concentrations (*c*) indicated in g/100 mL. The measurements were carried out in a cell with a path length (l) of 10 cm. Specific rotations $[\alpha]_D$ were calculated using the equation $[\alpha]_D = 100.\alpha/(c.l)$ and are given in 0.1 deg * cm^2 * g^{-1}.

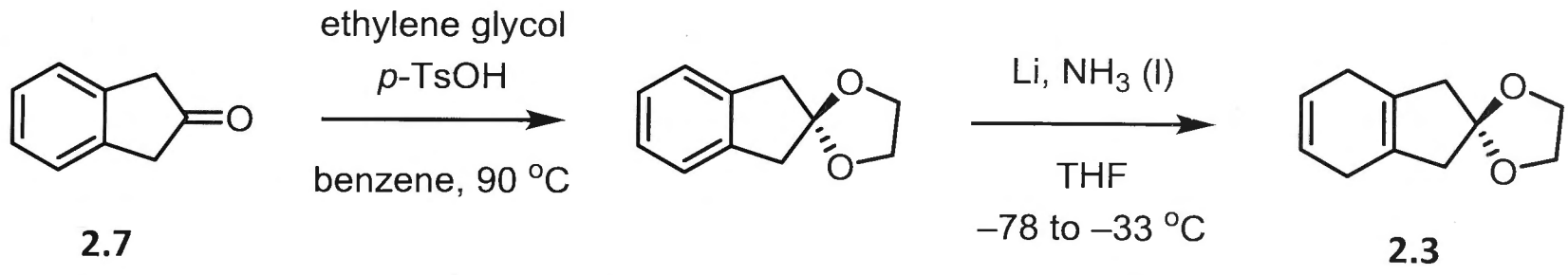
Melting points were measured on a Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected.

Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and by treatment with a suitable dip followed by heating. These dips included a mixture of vanillin : sulfuric acid : ethanol (1 g : 1 g : 18 mL) or phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL). The retardation factor (R_f) values cited here have been rounded to the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still *et al.*[1] with silica gel 60 (0.040-0.063 mm) as the stationary phase, and using the analytical (AR) or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. THF, dichloromethane, acetonitrile, benzene and toluene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al.*[2] Spectroscopic grade solvents were used for all analyses. Where necessary, reactions were performed under a nitrogen or argon atmosphere.

All microwave irradiation experiments were carried out in a CEM Explorer™ microwave apparatus operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W utilising the standard absorbance level of 300 W maximum power. The reactions were carried out in 10 mL Pyrex vials sealed with CEM plastic crimp tops and equipped with a magnetic stirrer. The temperature was measured with an infrared sensor on the outer surface of the process vial. After the irradiation period, the reaction vial was cooled rapidly (2 min) to ambient temperature using a nitrogen jet.

6.2. Experimental Part for Chapter 2

1',3',4',7'-Tetrahydrospiro[(1,3)dioxolane-2,2'-indene] (2.3)



2.7 **2.3**

Following a procedure reported by Birch,[3] a magnetically stirred solution of 2-indanone (**2.7**) (6.00 g, 45.43 mmol) in benzene (150 mL) was subjected to reaction with ethylene glycol (12.7 mL, 227.2 mmol) and *p*-toluenesulfonic acid (1.30 g, 6.82 mmol). The reaction mixture was heated at reflux until the expected amount of water had deposited in the attached Dean-Stark trap and then allowed to cool to room temperature. The organic layer was washed with $NaHCO_3$ (15 mL of a sat. aq. solution), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product as a dark-green oil. Subjection of this material to flash column chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.4 in 9:1 v/v hexane/ethyl acetate) yielded the intermediate ketal (7.61 g, 95%) as a pale-green oil.

Intermediate ketal

^{1}H-NMR (300 MHz) δ 7.19 (m, 4H), 4.03 (s, 4H), 3.20 (s, 4H).

^{13}C-NMR (75 MHz) δ 139.7 (C), 126.6 (CH), 124.5 (CH), 117.5 (C), 64.4 (CH_2), 43.1 (CH_2).

IR ν_{max} 3025, 2881, 2849, 1427, 1101 cm^{-1}.

MS (EI, 70eV) *m/z* 176 ($M^{+\bullet}$, 10%), 169 (20), 131 (35), 119 (30), 69 (100).

HREIMS found: $M^{+\bullet}$, 176.0837. $C_{11}H_{12}O_2$ requires $M^{+\bullet}$, 176.0837.

A solution of the intermediate ketal (1.00 g, 5.68 mmol, obtained as described above) in THF (20 mL) was added to a dark-blue solution of lithium wire (*ca*. 200 mg, 28 g atom, washed) in liquid ammonia (100 mL) maintained at −78 °C. The reaction mixture was allowed to stand at reflux (−33 °C) for 2 h before being re-cooled to −78 °C, then treated with ethanol (*ca*. 10 mL) until the blue colour disappeared. The ammonia was allowed to evaporate overnight and the residue partitioned between diethyl ether (20 mL) and water (20 mL). The separated organic layer was washed with water (1 x 20 mL) and brine (1 x 20 mL), before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The milky-brown oil was crystallised from hexane to give the title 1,4-diene **2.3** (7.15 g, 94%) as a colourless, crystalline solid.

^{1}H-NMR (300 MHz) δ 5.71 (s, 2H), 3.94 (s, 4H), 2.61 (s, 4H), 2.52 (s, 4H).

^{13}C-NMR (75 MHz) δ 129.0 (C), 124.2 (CH), 115.9 (C), 64.1 (CH_2), 46.1 (CH_2), 26.9 (CH_2).

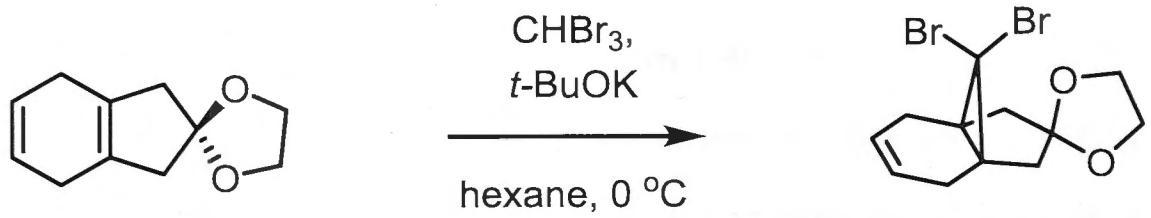
IR ν_{max} 2881, 2819, 1327 cm^{-1}.

MS (EI, 70eV) *m/z* 178 ($M^{+\bullet}$, 85%), 163 (20), 105 (40), 91 (65), 84 (90), 49 (100).

HREIMS found: $M^{+\bullet}$, 178.0993. $C_{11}H_{14}O_2$ requires $M^{+\bullet}$, 178.0994.

mp 44-45 °C (Lit. 43-44 °C).[3]

(3a*R*,7a*S*)-8,8-Dibromo-1,3,4,7-tetrahydrospiro[3a,7a-methanoindene-2,2'-(1,3)dioxolane] (2.8)



2.3 **2.8**

A magnetically stirred solution of ketal **2.3** (680 mg, 3.82 mmol) and bromoform (0.52 mL, 5.9 mmol) in hexane (40 mL) maintained at 0 °C was treated, in 200 mg portions every 0.3 h, with *t*-BuOK (1.20 g, 9.83 mmol). Stirring was continued at 0 °C for 7 h and then the reaction mixture was allowed to warm to room temperature before being quenched with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash column chromatography (silica, 17:3 v/v pentane/diethyl ether elution) to give two fractions, A and B.

Concentration of fraction **A** (R_f = 0.5 in 3:1 v/v hexane/ethyl acetate) yielded compound **2.3** (168 mg, 25% recovery) as a colourless, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.6 in 3:1 v/v hexane/ethyl acetate) yielded the *title propellane* ***2.8*** (731 mg, 73% brsm) as an off-white solid.

^{1}H-NMR (300 MHz) δ 5.59 (s, 2H), 3.86 (m, 4H), 2.47 (m, 8H).

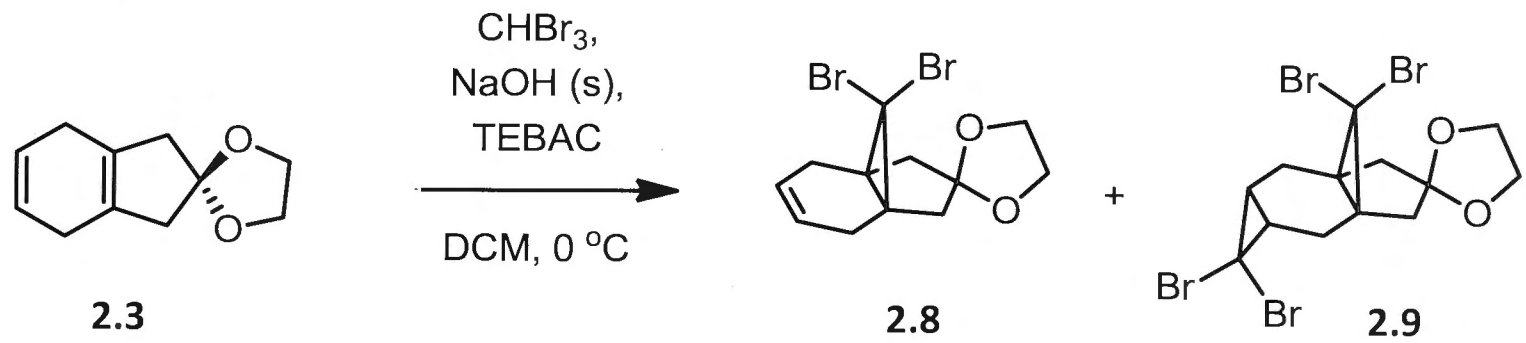
^{13}C-NMR (75 MHz) δ 123.2 (CH), 121.6 (C), 65.1 (CH_2), 63.6 (CH_2), 60.1 (C), 49.8 (CH_2), 33.3 (C), 28.6 (CH_2).

MS (EI, 70eV) *m/z* 350 ($M^{+\bullet}$, 20%), 269 (30), 178 (100), 117 (30), 105 (60), 91 (95).

HREIMS found: $M^{+\bullet}$, 347.9364. $C_{12}H_{14}{}^{79}Br_2O_2$ requires $M^{+\bullet}$, 347.9361.

mp 89-94 °C.

(1a*R*,2a*S*,5a*R*,6a*S*)-1,1,7,7-Tetrabromohexahydro-1*H*-spiro[2a,5a-methanocyclopropa-(*f*)indene-4,2'-(1,3)dioxolane] (2.9)



2.3 **2.8** **2.9**

A magnetically stirred solution of ketal **2.3** (250 mg, 1.41 mmol) in DCM (15 mL) was treated with bromoform (0.39 mL, 4.21 mmol), crushed NaOH pellets (0.34 g, 8.42 mmol) and TEBAC (5 mg, 0.056 mmol) and the resulting mixture heated to 40 °C for 4 h. The mixture thus obtained was allowed to cool to room temperature, filtered through Celite™ and the filtrate concentrated under reduced pressure. The resulting brown solid was subjected to flash column chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to give two fractions, A and B.

Concentration of fraction **A** (R_f = 0.3 in 9:1 v/v hexane/ethyl acetate) yielded propellane **2.8** (34 mg, 7%) as a pale-yellow solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.2 in 9:1 v/v hexane/ethyl acetate) yielded the *title bis-adduct* ***2.9*** (89 mg, 18%) as a pale-yellow solid.

Compound 2.9

^{1}H-NMR (400 MHz) δ 3.76 (s, 4H), 2.52 (d, *J* = 15.8 Hz, 2H), 2.38 (dd, *J* = 5.9, 2.6 Hz, 1H), 2.34 (dd, *J* = 5.9, 2.6 Hz, 1H), 2.30 (d, *J* = 15.8 Hz, 2H), 2.02 (d, *J* = 15.8 Hz, 2H), 1.83 (dd, *J* = 5.9, 2.9 Hz, 2H).

^{13}C-NMR (100 MHz) δ 120.4 (C), 64.4 (CH_2), 63.6 (CH_2), 53.1 (C), 51.4 (CH_2), 49.8 (C), 33.7 (C), 26.7 (CH), 23.8 (CH_2).

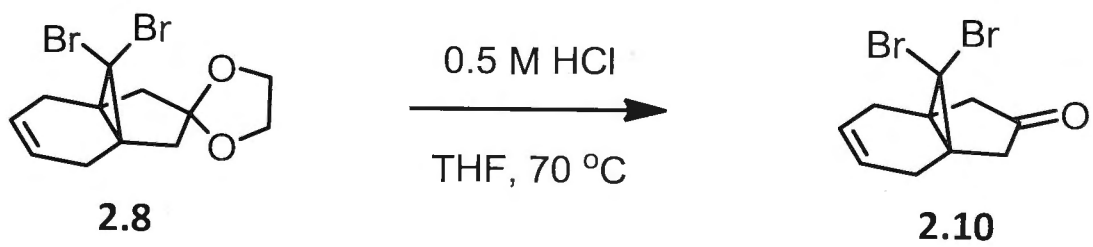
IR ν_{max} 2927, 2878, 1432 cm^{-1}.

MS (EI, 70eV) *m/z* 522 ($M^{+\bullet}$, <1%), 444 (15), 442 (50), 440 (50), 438 (20), 278 (30), 129 (45), 115 (35), 86 (100).

HREIMS found: $[M-Br]^{+\bullet}$, 440.8529. $C_{13}H_{14}{}^{79}Br_2{}^{81}BrO_2$ requires $[M-Br]^{+\bullet}$, 440.8523.

mp 153-158 °C.

(3a*R*,7a*S*)-8,8-Dibromo-4,7-dihydro-1*H*-3a,7a-methanoinden-2(3*H*)-one (2.10)



2.8 **2.10**

A magnetically stirred solution of propellane **2.8** (100 mg, 0.287 mmol) in THF (10 mL) was treated with HCl (0.4 mL of a 0.5 M aq. solution, 0.20 mmol) and the resulting mixture heated at reflux for 2 h, then cooled and quenched with $NaHCO_3$ (4 mL of a sat. aq. solution). The resulting mixture was extracted with diethyl ether (1 x 10 mL) and the separated organic layer washed with brine (1 x 5 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *title ketone* ***2.10*** (73 mg, 84%) as a colourless, crystalline solid. This material was used without further purification in the next step of the reaction sequence.

^{1}H-NMR (400 MHz) δ 5.65 (s, 2H), 2.85 (dd, *J* = 18.6, 2.1 Hz, 2H), 2.57 (dd, *J* = 18.6, 2.1 Hz, 2H), 2.50 (s, 4H).

^{13}C-NMR (100 MHz) δ 213.5 (CO), 123.1 (CH), 53.6 (C), 49.9 (CH_2), 29.7 (C), 27.2 (CH_2).

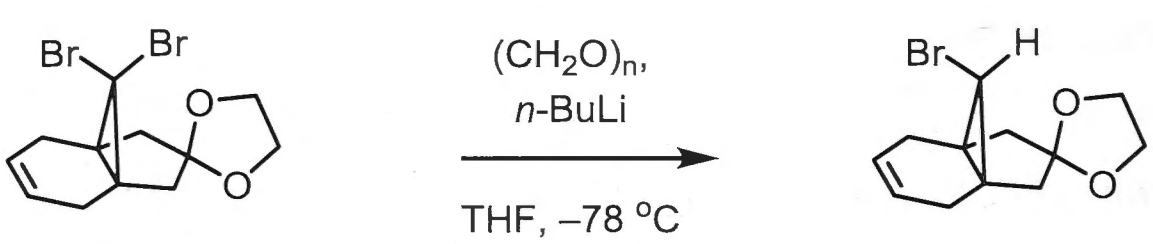
IR ν_{max} 3023, 2916, 2887, 1754 cm^{-1}.

MS (EI, 70eV) *m/z* 306 ($M^{+\bullet}$, 20%), 225 (35), 133 (70), 117 (100), 104 (55), 91 (90).

HREIMS found: $M^{+\bullet}$, 305.9078. $C_{12}H_{14}{}^{79}Br^{81}BrO_2$ requires $M^{+\bullet}$, 305.9078.

mp 87-96 °C.

(3a*R*,7a*S*,8*rs*)-8-Bromo-1,3,4,7-tetrahydrospiro[3a,7a-methanoindene-2,2'-{1,3}dioxolane] (2.21)



2.8 **2.21**

A magnetically stirred solution of propellane **2.8** (36 mg, 0.10 mmol) in THF (1 mL) was treated dropwise with *n*-BuLi (0.13 mL of a 1.6 M solution in hexane, 0.20 mmol) at −78 °C. Paraformaldehyde (5 mg, 0.18 mmol) was then added to the reaction mixture and stirring continued for 0.5 h. The ensuing mixture was allowed to warm to room temperature before being treated with HCl (5 mL of a 1 M aq. solution) and extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (1 x 10 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting yellow oil to flash column chromatography (silica, 3:1 v/v pentane/diethyl ether elution) afforded, after concentration of the appropriate fractions (R_f = 0.7 in 3:1 v/v hexane/ethyl acetate), the *title propellane* ***2.21*** (39 mg, 50%) as a clear, colourless oil.

^{1}H-NMR (400 MHz) δ 5.99 (s, 2H), 3.89 (t, *J* = 4.7 Hz, 2H), 3.78 (t, *J* = 4.7 Hz), 3.41 (s, 1H), 2.32 (d, *J* = 16.3 Hz, 2H), 2.22 (d, *J* = 14.1 Hz, 2H), 2.20 (d, *J* = 16.3 Hz, 2H), 2.15 (d, *J* = 14.1 Hz, 2H).

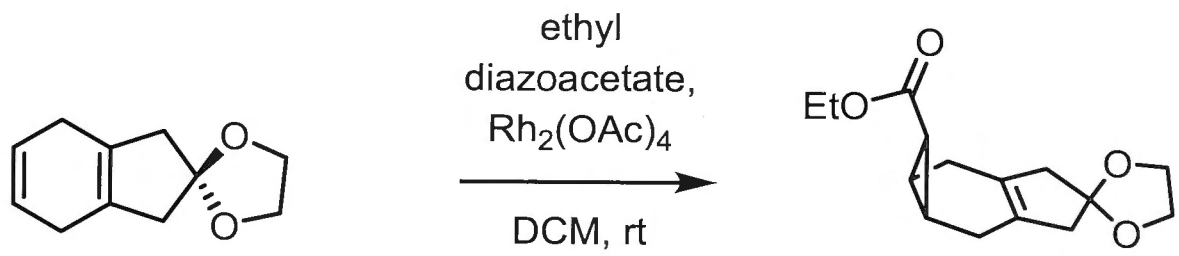
^{13}C-NMR (100 MHz) δ 123.9 (CH), 115.7 (C), 64.2 (CH_2), 64.1 (CH_2), 46.4 (CH_2), 36.5 (CH), 26.5 (CH_2), 24.4 (C).

IR ν_{max} 2882, 1430, 1103 cm^{-1}.

MS (EI, 70eV) *m/z* 272 ($M^{+\bullet}$, 10%), 270 (10), 191 (10), 117 (45), 91 (100).

HREIMS found: $M^{+\bullet}$, 271.0155. $C_{12}H_{14}{}^{81}BrO_2$ requires $M^{+\bullet}$, 271.0157.

Ethyl (1*rs*,1a*S*,6a*R*)-1a,2,3,5,6,6a-Hexahydro-1*H*-spiro[cyclopropa{f}indene-4,2'-{1,3}-dioxolane]-1-carboxylate (2.23)



2.7 **2.23**

A magnetically stirred solution of diene **2.7** (419 mg, 2.35 mmol) in DCM (10 mL) maintained at room temperature was treated with $Rh_2(OAc)_4$ (6 mg, 0.6 mol%) then with a solution of ethyl diazoacetate (0.23 mL, 2.3 mmol) in DCM (12 mL) which was added *via* syringe pump at a rate of 2 mL/h. The ensuing mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 9:1 v/v pentane/diethyl ether - diethyl ether gradient elution) to give two fractions, A and B.

Concentration of fraction **A** (R_f = 0.7 in 3:1 v/v hexane/ethyl acetate) yielded compound **2.7** (120 mg, 29% recovery). This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.5 in 3:1 v/v hexane/ethyl acetate) yielded the *title ester* ***2.23*** (298 mg, 69% brsm) as a pale-yellow oil.

Compound 2.23

^{1}H-NMR (300 MHz) δ 4.09 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 4H), 2.55 - 2.17 (complex m, 8H), 1.71 (m, 2H), 1.46 (t, *J* = 4.4 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H).

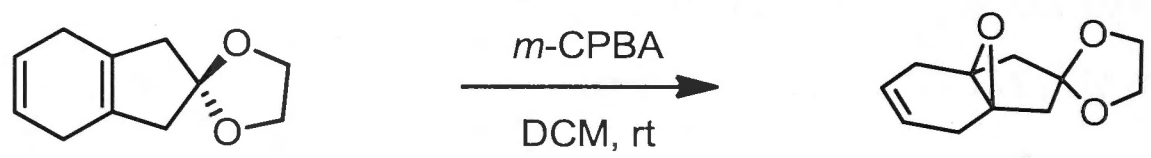
^{13}C-NMR (75 MHz) δ 174.7 (CO), 127.3 (C), 115.4 (C), 64.1 (CH_2), 60.2 (CH_2), 46.4 (CH_2), 23.7 (CH_2), 23.3 (CH), 21.5 (CH), 14.2 (CH_3).

IR ν_{max} 2981, 2899, 1752, 1720 cm^{-1}.

MS (EI, 70eV) *m/z* 264 ($M^{+\bullet}$, 100%), 219 (30), 191 (35), 117 (25), 91 (20).

HREIMS found: $M^{+\bullet}$, 264.1363. $C_{15}H_{20}O_4$ requires $M^{+\bullet}$, 264.1362.

(3a*R*,7a*S*)-1,3,4,7-Tetrahydrospiro[3a,7a-epoxyindene-2,2'-(1,3)dioxolane]



2.7

A magnetically stirred solution of diene **2.7** (29 mg, 0.16 mmol) in DCM (3 mL) maintained at room temperature was treated with *m*-CPBA (77%, 44 mg, 0.20 mmol). After 2 h the reaction mixture was quenched with water (3 mL), the layers separated and the organic phase concentrated under reduced pressure. Subjection of the resulting yellow oil to flash column chromatography (silica, 3:1 v/v pentane/diethyl ether elution) gave, after concentration of the appropriate fractions (R_f = 0.2 in 3:1 v/v hexane/ethyl acetate), the *title epoxide* as an inseparable 1:1 mixture with *m*-chlorobenzoic acid in near quantitative yield (based on the ^{1}H NMR spectrum).

Title Epoxide

^{1}H-NMR (300 MHz) δ 5.49 (d, *J* = 2.5 Hz, 2H), 3.94 (t, *J* = 9.5 Hz, 4H), 3.82 (t, *J* = 9.5 Hz, 4H), 2.62 (dd, *J* = 16.6, 2.5 Hz, 2H), 2.41 (d, *J* = 16.6 Hz, 2H), 2.34 (d, *J* = 14.8 Hz, 2H), 2.10 (d, *J* = 14.8 Hz, 2H).

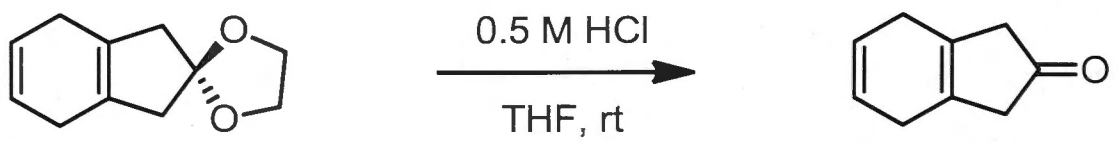
^{13}C-NMR (75 MHz) δ 121.9 (CH), 114.1 (C), 64.5 (CH_2), 64.2 (CH_2), 63.4 (C), 43.4 (CH_2), 27.3 (CH_2).

IR Obscured by *m*-chlorobenzoic acid residues.

MS (EI, 70eV) *m/z* 194 ($M^{+\bullet}$, 5%), 156 (100), 139 (98), 111 (55).

HREIMS found: $M^{+\bullet}$, 194.0944. $C_{11}H_{14}O_3$ requires $M^{+\bullet}$, 194.0943.

4,7-Dihydro-1*H*-inden-2(3*H*)-one (2.27)



2.7 **2.27**

A magnetically stirred solution of ketal **2.7** (85 mg, 0.48 mmol) in THF (5 mL) was treated with HCl (0.6 mL of a 0.5 M aq. solution, 0.28 mmol) and the ensuing mixture stirred at room temperature for 2 h then quenched with $NaHCO_3$ (4 mL of a sat. aq. solution) and extracted with diethyl ether (1 x 5 mL). The separated organic layer was washed with brine (1 x 5 mL), before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash column chromatography (silica, 9:1 v/v pentane/diethyl ether elution) afforded two fractions, A and B.

Concentration of fraction **A** (R_f = 0.5 in 3:1 v/v hexane/ethyl acetate) gave compound **2.7** (35 mg, 41% recovery) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.4 in 3:1 v/v hexane/ethyl acetate) yielded the *title compound* ***2.27*** (31 mg, 82% brsm) as a clear, colourless oil.

Compound 2.27

^{1}H-NMR (300 MHz) δ 5.79 (s, 2H), 2.82 (s, 4H), 2.72 (s, 4H).

^{13}C-NMR (75 MHz) δ 215.9 (CO), 129.8 (C), 124.3 (CH), 64.5 (CH_2), 26.8 (CH_2).

IR ν_{max} 3069, 2927, 2252, 1726, 1628 cm^{-1}.

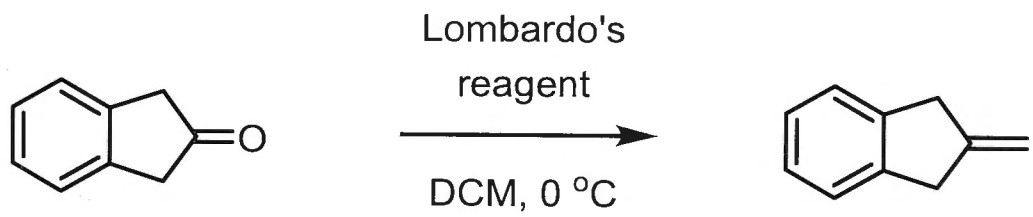
MS (EI, 70eV) *m/z* 134 ($M^{+\bullet}$, 20%), 117 (15), 104 (85), 91 (100).

HREIMS found: $M^{+\bullet}$, 134.0731. $C_9H_{10}O$ requires $M^{+\bullet}$, 134.0732.

Lombardo's Reagent (CH_2Br_2-Zn-TiCl)

Lombardo's reagent was prepared following a literature procedure.[4] Thus, a magnetically stirred suspension of activated zinc dust[5] (2.66 g, 40.7 mmol) and dibromomethane (0.9 mL, 12.8 mmol) in THF (24 mL) maintained at −40 °C was treated, dropwise, with titanium tetrachloride (1 mL) and thereby generating a grey-green suspension that was allowed to warm to 5 °C then stirred at this temperature for 20 h, after which time it was cooled to 0 °C and DCM (5 mL) was added to give a thick light grey slurry. This slurry, which was *ca*. 0.3 M in the title reagent, was either used immediately or stored at −20 °C for up to three days. A darkening in the colour indicated decomposition of the reagent.

2-Methylene-2,3-dihydro-1*H*-indene (2.51)



2.7 **2.51**

A magnetically stirred solution of 2-indanone **2.7** (500 mg, 3.78 mmol) in DCM (8 mL) maintained at 0 °C was treated with Lombardo's reagent (16.5 mL, 1.3 mol equiv.). After 2.5 h more reagent (5 mL) was added and the ensuing mixture stirred at room temperature for 22 h before being diluted with hexane (50 mL) then quenched with a mixture of brine (25 mL) and $NaHCO_3$ (25 mL of a sat. aq. solution) (CAUTION: strong effervescence). The resulting slurry was stirred for 0.5 h and the separated aqueous layer extracted with hexane (2 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) before being dried ($MgSO_4$),

filtered, and concentrated under reduced pressure. Subjection of the resulting yellow oil to flash column chromatography (silica, hexane – 8:1 v/v pentane/diethyl ether gradient elution) yielded two fractions, A and B.

Concentration of fraction **A** (R_f = 0.6 in hexane) yielded the *title indene* ***2.51*** (194 mg, 44% brsm) as a clear, colourless oil.

^{1}H-NMR (300 MHz) δ 7.21 (m, 2H), 7.18 (m, 2H), 5.10 (m, 2H), 3.71 (t, *J* = 2.3 Hz, 4H).

^{13}C-NMR (75 MHz) δ 148.6 (C), 142.3 (C), 126.4 (CH), 124.4 (CH), 107.8 (CH_2), 39.4 (CH_2).

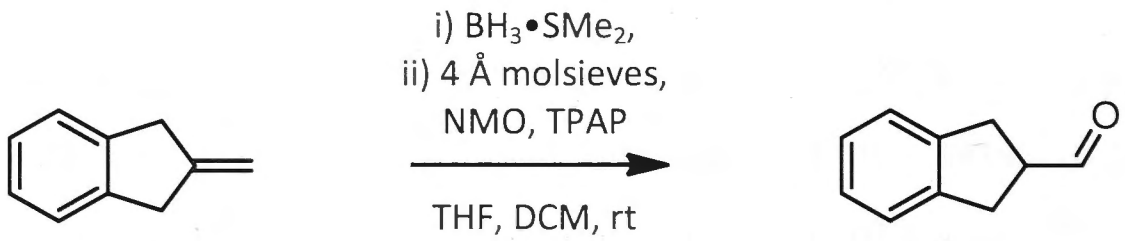
IR ν_{max} 3070, 3021, 2925, 2853, 1459 cm^{-1}.

MS (EI, 70eV) *m/z* 130 ($M^{+\bullet}$, 95%), 129 (100), 115 (70).

HREIMS found: $M^{+\bullet}$, 130.0783. $C_{10}H_{10}$ requires $M^{+\bullet}$, 130.0783.

Concentration of fraction **B** (R_f = 0.5 in 17:3 v/v hexane/ethyl acetate) yielded compound **2.7** (50 mg, 10% recovery). This material was identical, in all respects, with an authentic sample.

2,3-Dihydro-1*H*-indene-2-carbaldehyde (2.28)



2.51 **2.28**

A magnetically stirred solution of indene **2.51** (460 mg, 3.53 mmol) in THF (15 mL) was treated with a solution of borane-dimethyl sulfide complex (2.1 mL of a 2 M solution in THF, 3.89 mmol) and the resulting mixture stirred at room temperature for 22 h before being diluted with DCM (10 mL). Activated 4 Å molecular sieves (spatula tip) and NMO (1.24 g, 10.6 mmol) were then added to the reaction mixture and after 1 h TPAP (62 mg, 0.177 mmol) was also added. The ensuing mixture was stirred at room temperature until the colour changed from green to black. After another 0.33 h the reaction mixture was filtered through a short plug of TLC grade silica gel. The filtrate was stirred for 0.2 h in the presence of activated charcoal (spatula tip) then filtered through Celite™ and the filtrate concentrated under reduced pressure. Subjection of the resulting yellow oil to flash column chromatography (silica, pentane - 8:2 v/v pentane/diethyl ether gradient elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.6 in hexane) yielded compound **2.51** (42 mg, 9% recovery). This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.4 in 17:3 v/v hexane/ethyl acetate) yielded the title aldehyde **2.28**[6] (245 mg, 52% brsm) as a clear, colourless oil.

Compound 2.28

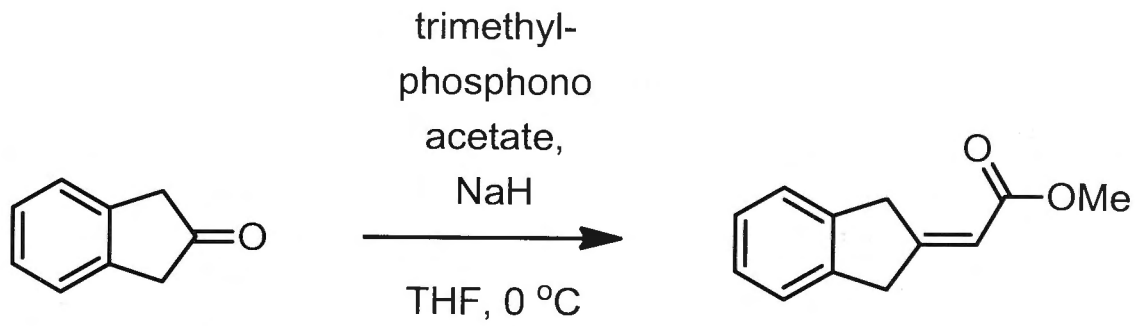
^{1}H-NMR (300 MHz) δ 9.78 (d, *J* = 1.5 Hz, 1H), 7.23 (m, 2H), 7.18 (m, 2H), 3.30 (m, 2H), 3.29 (partially obscured, 1H), 3.20 (m, 2H).

^{13}C-NMR (75 MHz) δ 202.8 (CO), 141.1 (C), 126.8 (CH), 124.6 (CH), 50.6 (CH), 32.9 (CH_2).

MS (EI, 70eV) *m/z* 146 ($M^{+\bullet}$, 70%), 128 (20), 115 (100), 91 (25).

These data matched those reported by Winter *et al.*[6]

Methyl 2-(1*H*-inden-2[3*H*]-ylidene)acetate (2.55)



2.7 **2.55**

Following the procedure of Ksander,[7] a magnetically stirred a suspension of NaH (1.31 g of a 60% dispersion in mineral oil, 54.5 mmol) in THF (45 mL) was cooled to 0 °C and trimethyl phosphonoacetate (8.8 mL, 9.92 g, 54.5 mmol) added dropwise. The resulting thick white suspension was stirred at room temperature for 0.5 h and then cooled to 0 °C before being treated, dropwise, with a solution of 2-indanone (**2.7**) (3.00 g, 22.7 mmol) in THF (45 mL). The ensuing brown reaction mixture was stirred at room temperature for 1 h then poured into brine (100 mL) and extracted with diethyl ether (2 x 40 mL). The combined organic phases were washed with brine (1 x 100 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting brown oil to flash chromatography (silica, pentane - 7:3 v/v pentane/diethyl ether gradient elution) afforded, after concentration of the appropriate fractions (R_f = 0.4 in 17:3 v/v hexane/ethyl acetate), the title ester **2.55**[7] (4.18 g, 98%) as a colourless, crystalline solid.

^{1}H-NMR (300 MHz) δ 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 4.0 Hz, 1H), 7.24 (t, *J* = 8.0, 1H), 7.15 (m, 1H), 6.70 (s, 1H), 3.72 (s, 3H), 3.54 (s, 2H), 3.45 (s, 2H).

^{13}C-NMR (75 MHz) δ 171.4 (CO), 144.7 (C), 143.4 (C), 140.9 (C), 130.1 (CH), 126.3 (CH), 124.4 (CH), 123.5 (CH), 120.6 (CH), 52.0 (CH_3), 41.3 (CH_2), 36.8 (CH_2).

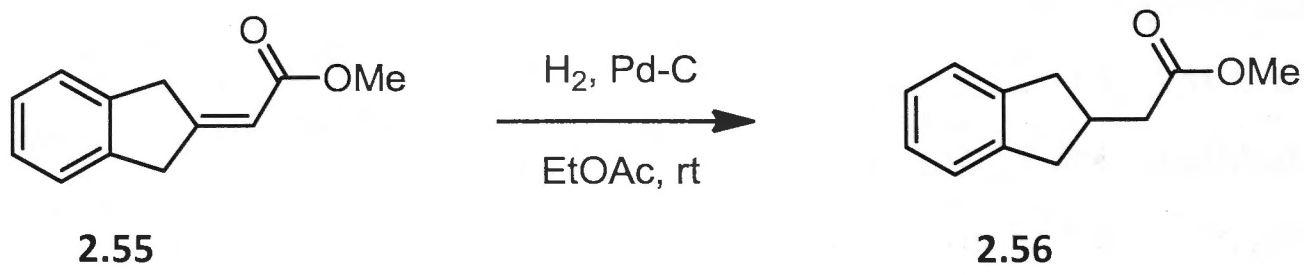
IR ν_{max} 3056, 3020, 2923, 1740 cm^{-1}.

MS (EI, 70eV) *m/z* 188 ($M^{+\bullet}$, 30%), 149 (15), 129 (100), 83 (35).

HREIMS found: $M^{+\bullet}$, 188.0835. $C_{12}H_{12}O_2$ requires $M^{+\bullet}$, 188.0837.

mp 87-89 °C (Lit. oil).[7]

Methyl 2-(2,3-dihydro-1*H*-inden-2-yl)acetate (2.56)



2.55 **2.56**

A magnetically stirred solution of the α,β-unsaturated ester **2.55** (4.18 g, 22.2 mmol) in ethyl acetate (100 mL) was treated with 10% palladium on carbon (1.18 g) and the flask containing the resulting mixture was degassed and then filled with hydrogen three times. The ensuing mixture was allowed to stir vigorously under an atmosphere of hydrogen at room temperature for 5 h then filtered through Celite™. The filtrate was concentrated under reduced pressure to give the title ester **2.56**[7] (4.22 g, 99%) as a colourless, crystalline solid.

^{1}H-NMR (300 MHz) δ 7.22-7.10 (complex m, 4H), 3.70 (s, 3H), 3.15 (dd, *J* = 20.0, 10.4 Hz, 2H), 2.89 (m, 1H), 2.65 (dd, *J* = 20.0, 10.4 Hz, 2H), 2.51 (d, *J* = 10.4 Hz, 2H).

^{13}C-NMR (75 MHz) δ 173.4 (CO), 142.6 (C), 126.3 (CH), 124.4 (CH), 51.5 (CH_3), 39.7 (CH_2), 38.9 (CH_2), 36.1 (CH).

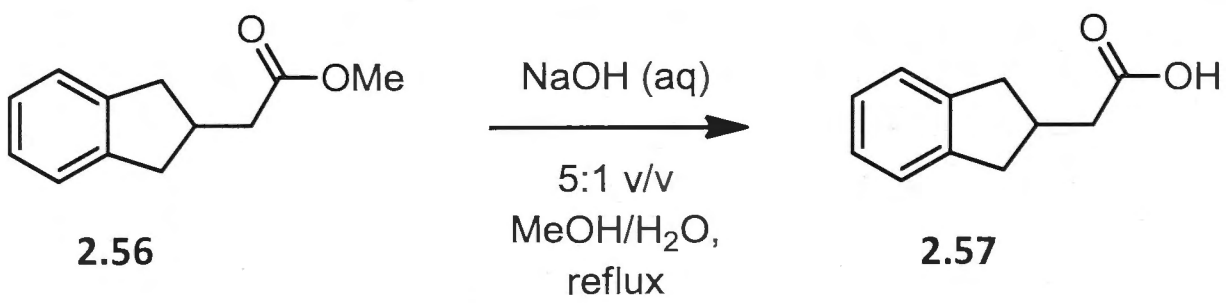
IR ν_{max} 3022, 2926, 1739 cm^{-1}.

MS (EI, 70eV) *m/z* 190 ($M^{+\bullet}$, 20%), 116 (100), 84 (60).

HREIMS found: $M^{+\bullet}$, 190.0991. $C_{12}H_{14}O_2$ requires $M^{+\bullet}$, 190.0994.

mp 32-35 °C (Lit. 33-34 °C).[8]

2-(2,3-Dihydro-1*H*-inden-2-yl)acetic acid (2.57)



2.56 **2.57**

A magnetically stirred solution of methyl ester **2.56** (3.96 g, 20.8 mmol) in 5:1 v/v MeOH/H_2O (30 mL) was treated with NaOH (10 mL of a 2 M aq. solution) and the resulting mixture heated at reflux for 0.5 h, then cooled to 0 °C, diluted with ethyl acetate (50 mL) and quenched with HCl (25 mL of a 1 M aq. solution). The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers washed with brine (1 x 15 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the *title acid* ***2.57*** (3.66 g, 99%) (R_f = 0.4 in 13:7 v/v hexane/ethyl acetate) as a colourless, crystalline solid. The crude product was used without further purification in the next step of the reaction sequence.

^{1}H-NMR (300 MHz) δ 10.50 (s, 1H, OH), 7.22-7.13 (complex m, 4H), 3.18 (dd, *J* = 15.3, 7.6 Hz, 2H), 2.90 (m, 1H), 2.68 (dd, *J* = 15.3, 7.6 Hz, 2H), 2.56 (d, *J* = 18.1 Hz, 2H).

^{13}C-NMR (75 MHz) δ 179.3 (CO), 142.5 (C), 126.3 (CH), 124.5 (CH), 39.7 (CH_2), 38.9 (CH_2), 35.8 (CH).

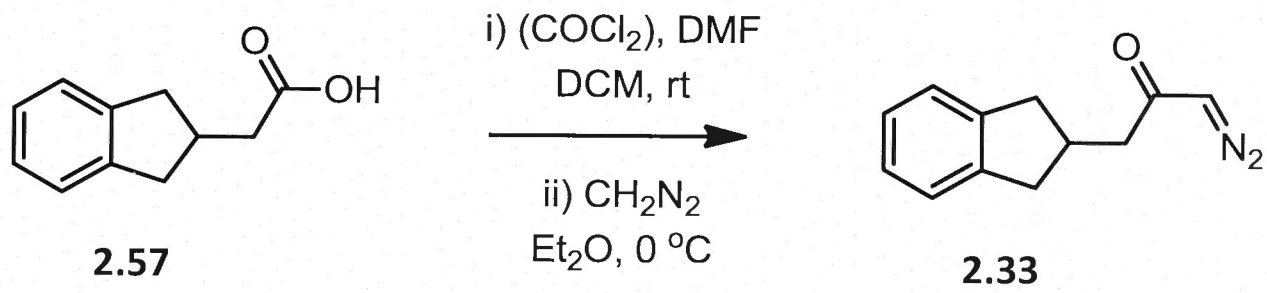
IR ν_{max} 3400, 3024, 2936, 2896, 2840, 2660, 1693 cm^{-1}.

MS (EI, 70eV) *m/z* 176 ($M^{+\bullet}$, 20%), 128 (5), 116 (100), 91 (5).

HREIMS found: $M^{+\bullet}$, 176.0838. $C_{11}H_{12}O_2$ requires $M^{+\bullet}$, 176.0837.

mp 87-90 °C (Lit. 85-88 °C).[9]

1-Diazo-3-(2,3-dihydro-1*H*-inden-2-yl)propan-2-one (2.33)



2.57 **2.33**

In a smooth-jointed round bottom flask a solution of carboxylic acid **2.57** (317 mg, 1.80 mmol) in DCM (10 mL) was treated with one drop of DMF, then oxalyl chloride (152 µL, 1.80 mmol) and the ensuing mixture stirred at room temperature for 1.5 h, then cooled to 0 °C and treated - dropwise at first, then more quickly - with a freshly distilled solution of diazomethane (CAUTION – explosive) in diethyl ether (7.2 mL of a *ca*. 0.3 M solution, 2.16 mmol). After the gas evolution had dissipated the reaction mixture was stirred for 0.5 h and then flushed with nitrogen to remove excess diazomethane before being concentrated to dryness. The resulting yellow oil was subjected to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) to yield, after concentration (CAUTION – diazo-compounds are potentially explosive) of the appropriate fractions (R_f = 0.3 in 3:1 v/v hexane/ethyl acetate), the *title diazoketone* ***2.33*** (286 mg, 80%) as a bright-yellow oil.

^{1}H-NMR (300 MHz) δ 7.17 (m, 4H), 5.27 (s, 1H), 3.15 (dd, *J* = 15.9, 7.7 Hz, 2H), 2.93 (m, 1H), 2.64 (dd, *J* = 15.9, 7.7 Hz, 2H), 2.49 (d, *J* = 6.6 Hz, 2H).

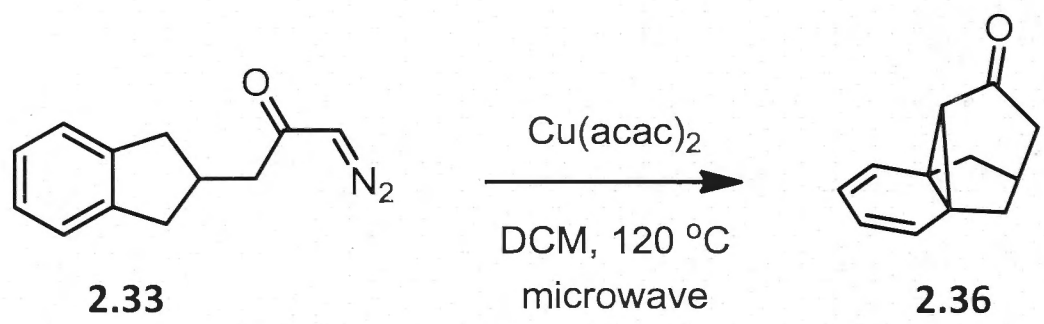
^{13}C-NMR (75 MHz) δ 194.3 (CO), 142.5 (C), 126.3 (CH), 124.5 (CH), 54.8 (CN_2), 46.4 (CH_2), 38.9 (CH_2), 36.2 (CH).

IR ν_{max} 3072, 2936, 2841, 2103, 1726, 1640, 1362 cm^{-1}.

MS (EI, 70eV) *m/z* 200 ($M^{+\bullet}$, 1%), 172 (60), 128 (100), 117 (75), 91 (85).

HREIMS found: $M^{+\bullet}$, 200.0956. $C_{12}H_{12}N_2O$ requires $M^{+\bullet}$, 200.0950.

(2*r*,4a*s*,4b*R*,8a*S*)-2,3-Dihydro-1*H*-2,4b-methanocyclopropa[1,2:1,3]dibenzen-4(4a*H*)-one (2.36)



2.33 **2.36**

A dry microwave tube equipped with stirrer bar was charged with a solution of diazo-compound **2.33** (20 mg, 0.10 mmol) in DCM (2.5 mL) whilst being maintained under a nitrogen atmosphere. $Cu(acac)_2$ (2 mg, 7 mol%) was then added and the tube sealed and immediately heated to 100 °C in the microwave for 2 min. (plus 2 min. ramp time) before being allowed to cool to room temperature. The resulting mixture was concentrated under reduced pressure and the residue subjected to flash column chromatography (silica, 7:3 v/v pentane/diethyl ether elution) to yield, after concentration of the appropriate fractions (R_f = 0.3 in 3:1 v/v hexane/ethyl acetate), the *title propelladiene* ***2.36*** (6 mg, 35%) as a colourless, crystalline solid.

^{1}H-NMR (300 MHz) δ 6.21 (dd, *J* = 7.7, 4.5 Hz, 2H), 5.98 (dd, *J* = 7.7, 4.5 Hz, 2H), 2.22 (m, 1H), 2.14 (d, *J* = 3.1 Hz) 2H, 1.98 (m, 4H), 0.90 (s, 1H).

^{13}C-NMR (75 MHz) δ 210.1 (CO), 127.2 (CH), 122.8 (CH), 43.7 (CH_2), 42.6 (CH), 39.0 (CH_2), 35.9 (C), 26.5 (CH).

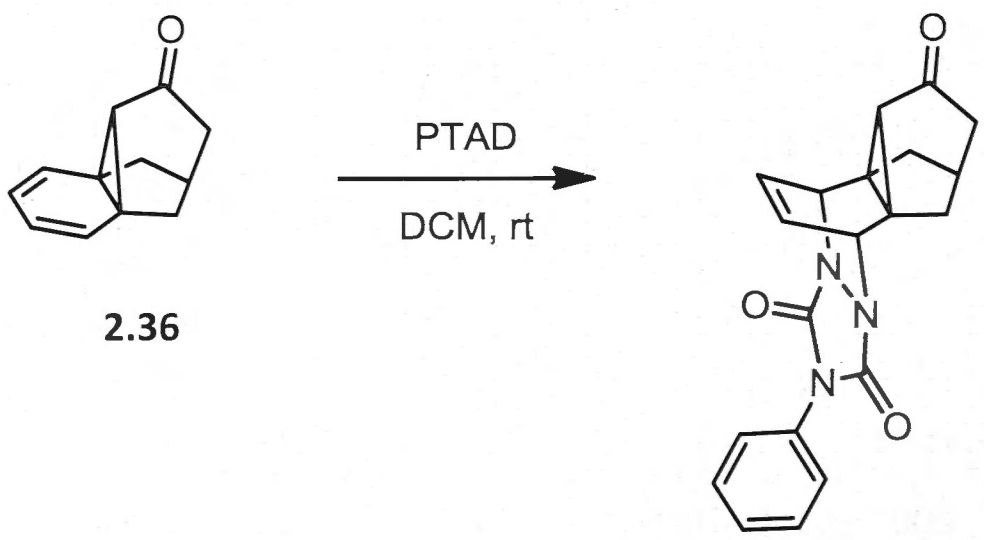
IR ν_{max} 3033, 2932, 2866, 1683 cm^{-1}.

MS (EI, 70eV) *m/z* 172 ($M^{+\bullet}$, 40%), 129 (100), 116 (30), 84 (30).

HREIMS found: $M^{+\bullet}$, 172.0892. $C_{12}H_{12}O$ requires $M^{+\bullet}$, 172.0888.

mp 66-70 °C.

(1*R*,7a*S*,7b*S*,10*R*,11a*R*)-4-Phenyl-7b,9,10,11-tetrahydro-1,7-etheno-7a,10-methanobenzo-[1,3]cyclopropa[1,2-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-3,5,8(1*H*,4*H*,7*H*)-trione



2.36

A magnetically stirred solution of propelladiene **2.36** (10 mg, 0.058 mmol) in DCM (0.5 mL) was treated with PTAD (15 mg, 0.087 mmol) and the resulting bright-pink reaction mixture stirred

at room temperature for 0.33 h. The ensuing mixture was concentrated under reduced pressure and subjection of the resulting brown solid to flash column chromatography (silica, 1:1 v/v PS 30-40/diethyl ether elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.3 in 1:1 v/v hexane/ethyl acetate) yielded the *title Diels-Alder adduct* as a colourless, amorphous solid (14 mg, 87% brsm).

Title Diels-Alder adduct

^{1}H-NMR (300 MHz) δ 7.33-7.50 (complex m, 5H), 6.22 (dd, *J* = 4.2, 3.5 Hz, 2H), 5.23 (t, *J* = 3.5 Hz, 2H), 2.63 (m, 1H), 2.39 (dd, *J* = 12.3, 5.4 Hz, 2H), 2.14 (d, *J* = 2.9 Hz, 2H), 2.05 (s, 1H), 1.73 (d, *J* = 12.3 Hz, 2H).

^{13}C-NMR (75 MHz) δ 205.6 (CO), 157.0 (CO), 129.2 (C), 128.5 (CH), 126.1 (CH), 125.6 (CH), 55.9 (CH), 43.5 (CH_2), 39.0 (CH_2), 32.4 (C), 30.2 (CH), 28.7 (CH).

IR ν_{max} 3020, 2941, 2873, 1779, 1713, 1694 cm^{-1}.

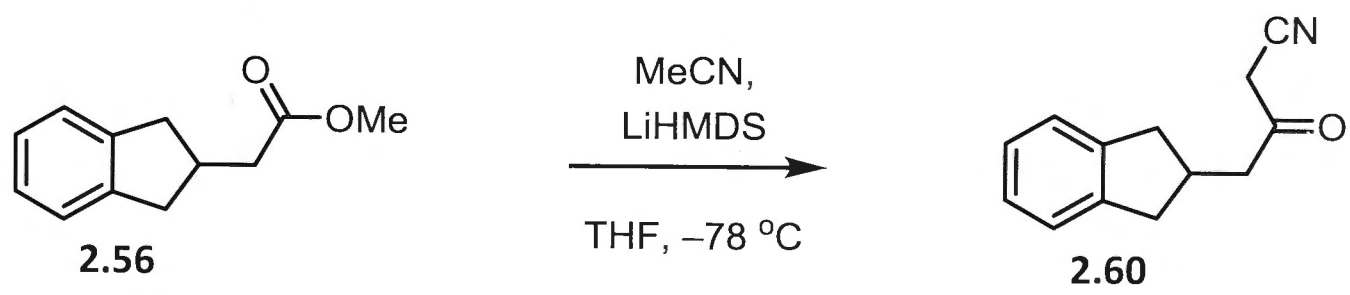
MS (EI, 70eV) *m/z* 347 ($M^{+\bullet}$, 20%), 172 (70), 129 (100), 116 (28).

HREIMS found: $M^{+\bullet}$, 347.1273. $C_{20}H_{17}N_3O_3$ requires $M^{+\bullet}$, 347.1270.

mp decomposition at 226 °C.

Concentration of fraction **B** (R_f = 0.3 in 1:1 v/v hexane/ethyl acetate) gave compound **2.36** (2 mg, 20% recovery). This material was identical, in all respects, with an authentic sample.

4-(2,3-Dihydro-1*H*-inden-2-yl)-3-oxobutanenitrile (2.61)



2.56 **2.60**

LiHMDS (2.1 mL of 1 M solution in THF, 2.10 mmol) was added to THF (6 mL) and the resulting solution stirred magnetically while being cooled to −78 °C under a nitrogen atmosphere. Dry acetonitrile (82 mL, 1.58 mmol) was then added dropwise to this solution and after 1 h a solution of the ester **2.56** (200 mg, 1.05 mmol) in THF (4 mL) was added slowly. The ensuing mixture was allowed to warm to room temperature and stirring continued under these conditions for 16 h before being treated sequentially with diethyl ether (10 mL), HCl (5 mL of a 1 M aqueous solution), and then brine (10 mL). The separated aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined organic phases washed with brine (2 x 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of

the ensuing pale-yellow oil to flash column chromatography (silica, 1:1 v/v PS 30-40/diethyl ether elution) afforded, after concentration of the appropriate fractions (R_f = 0.1 in 17:3 v/v hexane/ethyl acetate), the *title β-ketonitrile* ***2.60*** (205 mg, 98%) as a colourless, crystalline solid.

^{1}H-NMR (300 MHz) δ 7.12-7.22 (complex m, 4H), 3.46 (s, 2H), 3.19 (dd, *J* = 20.4, 9.6 Hz, 2H), 2.94 (m, 1H), 2.82 (d, *J* = 9.6 Hz, 2H), 2.59 (dd, *J* = 20.4, 8.8 Hz, 2H).

^{13}C-NMR (75 MHz) δ 196.8 (CO), 142.1 (C), 126.5 (CH), 124.5 (CH), 113.7 (CN), 47.8 (CH_2), 38.8 (CH_2), 34.5 (CH_2), 32.2 (CH).

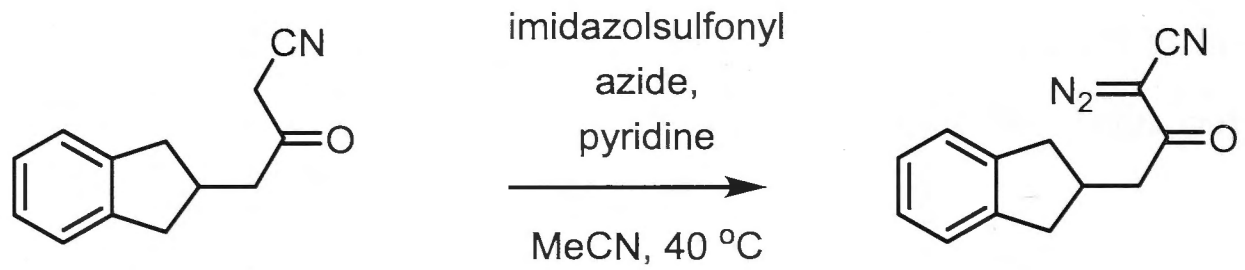
IR ν_{max} 3026, 2920, 2258, 1729 cm^{-1}.

MS (EI, 70eV) *m/z* 199 ($M^{+\bullet}$, 2%), 129 (5), 116 (100), 91 (6).

HREIMS found: $M^{+\bullet}$, 199.1000. $C_{13}H_{13}NO$ requires $M^{+\bullet}$, 199.0997.

mp 107-108 °C.

2-Diazo-4-(2,3-dihydro-1*H*-inden-2-yl)-3-oxobutanenitrile (2.34)



2.60 **2.34**

A magnetically stirred solution of β-ketonitrile **2.60** (380 mg, 1.91 mmol) in acetonitrile (20 mL) was treated with imidazolesulfonyl azide (396 mg, 2.29 mmol) and pyridine (0.77 mL, 9.54 mmol) and the ensuing pale-yellow reaction mixture was heated at 40 °C for 20 h (CAUTION – diazo-compounds are potentially explosive – use blast shield) before being concentrated under reduced pressure to give an orange oil. Subjection of this material to flash column chromatography (silica, 3:2 v/v pentane/diethyl ether elution) gave, after concentration of the appropriate fractions (R_f = 0.7 in 13:7 v/v hexane/ethyl acetate), the *title diazo-β-ketonitrile* ***2.34*** (415 mg, 96%) as fine, yellow needles.

^{1}H-NMR (300 MHz) δ 7.12-7.22 (complex m, 4H), 3.17 (dd, *J* = 15.6, 8.0 Hz, 2H), 2.97 (m, 1H), 2.82 (d, *J* = 8.0 Hz, 2H), 2.66 (dd, *J* = 15.6, 8.0 Hz, 2H).

^{13}C-NMR (75 MHz) δ 189.5 (CO), 142.1 (C), 126.5 (CH), 124.5 (CH), 108.4 (CN), 44.9 (CH_2), 38.8 (CH_2), 35.5 (CH) (the signal due to the carbon bearing the diazo-function was not observed).

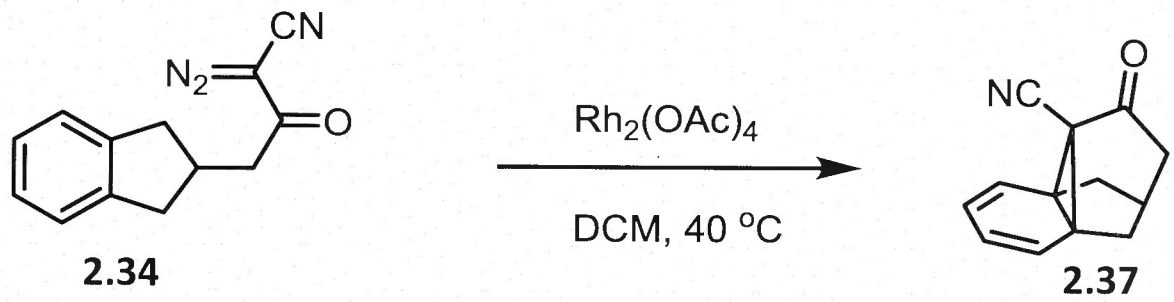
IR ν_{max} 2933, 2219, 2136, 1673 cm^{-1}.

MS (EI, 70eV) *m/z* 225 ($M^{+\bullet}$, 1%), 197 (15), 129 (15), 116 (100), 91 (22).

HREIMS found: $M^{+\bullet}$, 225.0908. $C_{13}H_{11}N_3O$ requires $M^{+\bullet}$, 225.0902.

mp 90 °C (loss of N_2 , forceful decomposition at 95 °C).

(2*s*,4a*r*,4b*R*,8a*S*)-4-Oxo-2,3,4,4a-tetrahydro-1*H*-2,4b-methanocyclopropa[1,2:1,3]dibenzene-4a-carbonitrile (2.37)



2.34 **2.37**

A magnetically stirred dispersion of $Rh_2(OAc)_4$ (5 mg, 0.011 mmol) in DCM (70 mL) was heated at reflux and then treated with a solution of diazo-β-ketonitrile **2.34** (1.03 g, 4.57 mmol) in DCM (100 mL) in 20 mL batches at a rate of 0.2 mmol h^{-1} (syringe pump). After addition was complete, the reaction mixture was cooled to room temperature and then concentrated under reduced pressure to give a white to purple coloured solid. Recrystallisation of this material (THF) gave the *title propelladiene* ***2.37*** (813 mg, 90%) as a colourless, crystalline solid.

^{1}H-NMR (300 MHz) δ 6.19 - 6.40 (m, 4H), 2.33 (m, 1H), 2.30 (m, 2H), 2.16 (apparent s, 4H).

^{13}C-NMR (75 MHz) δ 199.8 (CO), 127.1 (CH), 123.4 (CH), 112.2 (CN), 50.4 (CH_2), 43.2 (CH_2), 36.2 (C), 29.3 (C), 25.1 (CH).

IR ν_{max} 3050, 2979, 2953, 2873, 2238, 1698 cm^{-1}.

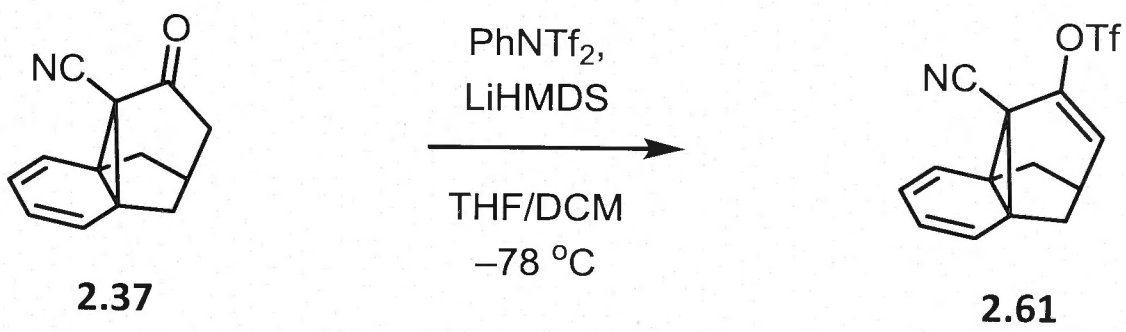
MS (EI, 70eV) *m/z* 197 ($M^{+\bullet}$, 70%), 153 (100), 128 (75), 115 (55).

HREIMS found: $M^{+\bullet}$, 197.0836. $C_{13}H_{11}NO$ requires $M^{+\bullet}$, 197.0841.

mp 194-200 °C.

X-ray (see Appendix 2).

(2*s*,4a*r*,4b*R*,8a*S*)-4a-Cyano-2,4a-dihydro-1*H*-2,4b-methanocyclopropa[1,2:1,3]dibenzen-4-yl trifluoromethanesulfonate (2.61)



2.37 **2.61**

A solution of propelladiene **2.37** (200 mg, 1.01 mmol) in DCM (3 mL) was added to THF (20 mL) and the resulting mixture stirred magnetically while being cooled to −78 °C and then treated, dropwise, with LiHMDS (1.42 mL of a 1 M solution in THF, 1.42 mmol). After a further 0.33 h *N*-

phenyl triflimide (471 mg, 1.32 mmol) was added in one portion and then the reaction mixture allowed to warm to room temperature and stirred for 16 h before being concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (silica, 7:3 - 1:9 v/v pentane/diethyl ether gradient elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.5 in 13:7 v/v hexane/ethyl acetate) gave the *title enol triflate* ***2.61*** (310 mg, 98% brsm) as a colourless, flaky solid.

Compound 2.61

^{1}H-NMR (400 MHz) δ 6.33 (m, 2H), 6.06 (m, 2H), 6.04 (d, *J* = 8.2 Hz, 1H), 2.67 (m, 1H), 1.88 (dd, *J* = 16.8, 6.4 Hz, 2H), 1.46 (d, *J* = 16.8 Hz, 2H).

^{13}C-NMR (100 MHz) δ 137.2 (C), 127.0 (CH), 120.9 (CH), 118.4 (q, *J* = 321 Hz, CF_3), 115.1 (CH), 112.0 (CN), 43.0 (C), 31.5 (CH_2), 26.6 (CH), 15.9 (C).

^{19}F-NMR (400 MHz) δ = −72.99 (s, 3H).

IR ν_{max} 2933, 2237, 1425, 1205, 1140 cm^{-1}.

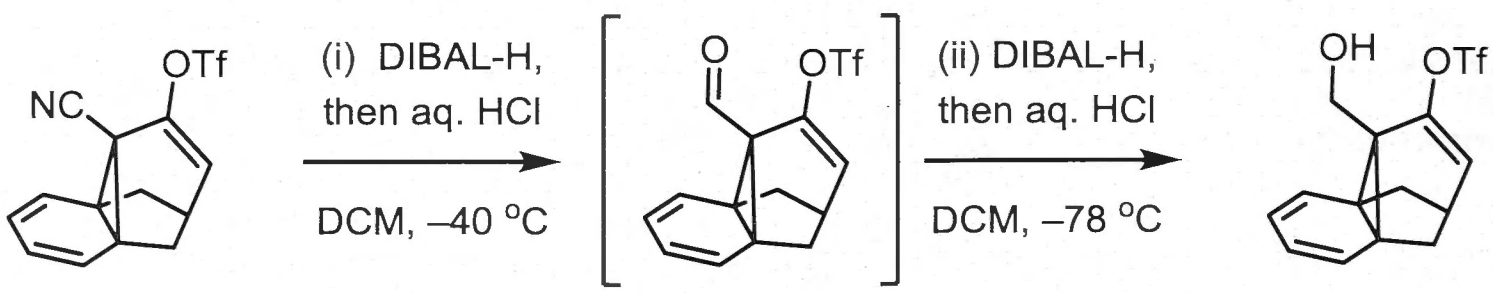
MS (EI, 70eV) *m/z* 329 ($M^{+\bullet}$, 20%), 225 (35), 196 (20), 168 (50), 141 (48), 92 (100).

HREIMS found: $M^{+\bullet}$, 329.0338. $C_{14}H_{10}F_3NO_3S$ requires $M^{+\bullet}$, 329.0333.

mp 79 °C (with decomposition).

Concentration of fraction **B** (R_f = 0.2 in 13:7 v/v hexane/ethyl acetate) gave compound **2.37** (10 mg, 5% recovery) as a pale-yellow, crystalline solid. This material was identical, in all respects, with an authentic sample.

(2*s*,4a*r*,4b*R*,8a*S*)-4a-(Hydroxymethyl)-2,4a-dihydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzen-4-yl trifluoromethanesulfonate (2.63)



2.61 **2.62** **2.63**

Step i. Under protection from light, a magnetically stirred solution of nitrile **2.61** (200 mg, 0.61 mmol) in DCM (5 mL) was cooled to −40 °C and then treated, dropwise, with DIBAL-H (1.2 mL of a 1 M solution in hexane, 1.22 mmol). The ensuing mixture was stirred at this temperature for 1 h before being treated with ethyl acetate (0.5 mL) and then allowed to warm to room temperature and quenched with HCl (1 mL of a 1 M aq. solution), a process that resulted in the development of a bright-yellow colouration in the organic phase which

thickened over time. The reaction mixture was stirred vigorously for 0.33 h and then the separated organic phase was concentrated under a stream of nitrogen. The resulting yellow oil was subjected to flash column chromatography (silica, 4:1 v/v pentane/diethyl ether elution) and concentration of the appropriate fractions (R_f = 0.9 in 13:7 v/v hexane/ethyl acetate) gave a bright-yellow oil that was immediately resubjected to treatment with DIBAL-H as specified in Step *ii*.

Step ii. A magnetically stirred solution of the bright-yellow oil obtained in *Step i* in DCM (5 mL) was cooled to −78 °C and then treated dropwise with DIBAL-H (1.8 mL of a 1 M solution in DCM) and the resulting mixture allowed to warm to room temperature over 16 h before being treated with ethyl acetate (0.5 mL) and then HCl (1 mL of a 1 M aq. solution). The resulting viscous mixture was diluted with DCM (5 mL) and then stirred vigorously for 0.5 h. The separated aqueous phase was extracted with DCM (2 x 4 mL) and the combined organic phases were then washed with water (1 x 5 mL) before bring dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash column chromatography (silica, 3:2 v/v pentane/diethyl ether elution) gave, after concentration of the appropriate fractions (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate), the *title alcohol* ***2.63*** (33 mg, 16%) as a colourless, crystalline solid.

^{1}H-NMR (300 MHz) δ 6.09 (m, 2H), 6.02 (m, 2H), 6.01 (d, *J* = 8.2 Hz, 1H), 3.63 (d, *J* = 5.3 Hz, 2H), 2.45 (m, 1H), 1.66 (dd, *J* = 16.4, 4.8 Hz, 2H), 1.47 (d, *J* = 16.4 Hz, 2H) (the signal due to the OH-group was not observed).

^{13}C-NMR (75 MHz) δ 143.9 (C), 125.2 (CH), 122.9 (CH), 118.4 (q, *J* = 320 Hz, CF_3), 115.7 (CH), 55.8 (CH_2), 37.5 (C), 33.2 (CH_2), 26.5 (CH), 23.1 (C).

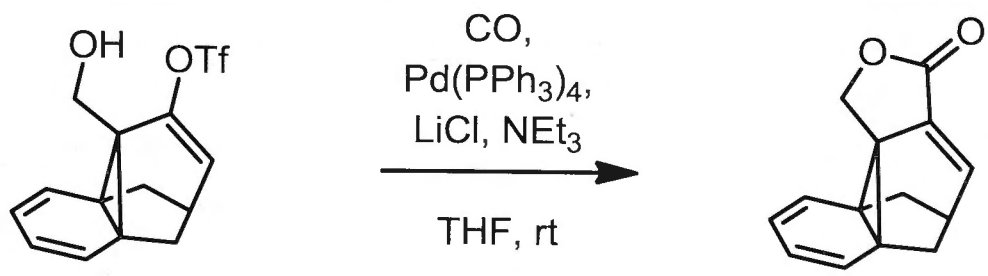
IR ν_{max} 3436, 3036, 2929, 2859, 1653, 1418 cm^{-1}.

MS (EI, 70eV) *m/z* 334 ($M^{+\bullet}$, 95%), 201 (20), 183 (45), 155 (85), 129 (100), 115 (85).

HREIMS found: $M^{+\bullet}$, 334.0487. $C_{14}H_{13}F_3O_4S$ requires $M^{+\bullet}$, 334.0487.

mp 54-57 °C.

(5*s*,6a*R*,10a*S*,10b*s*)-5,6-Dihydro-5,10a-methanobenzo[1,3]cyclopropa[1,2-*h*]isobenzo-furan-3(1*H*)-one (1.13)



2.63 **1.13**

A magnetically stirred solution of alcohol **2.63** (44 mg, 0.132 mmol) in THF (2.5 mL) was treated with $Pd(PPh_3)_4$ (15 mg, 0.0132 mmol, 10 mol%), LiCl (11 mg, 0.264 mmol), and triethylamine (73 μL, 0.526 mmol). The reaction flask was evacuated and then refilled with carbon monoxide three times before being stirred vigorously under an atmosphere of carbon monoxide at room temperature for 4 h. After this time the reaction mixture was sparged with nitrogen and then concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash column chromatography (silica, 7:3 v/v pentane/diethyl ether elution) gave, after concentration of the appropriate fractions (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate), the *title lactone* ***1.13*** (25 mg, 89%) as a colourless, crystalline solid.

^{1}H-NMR (400 MHz) δ 7.07 (d, *J* = 6.8 Hz, 1H), 6.14 (m, 2H), 5.92 (m, 2H), 3.89 (s, 2H), 2.90 (m, 1H), 1.74 (dd, *J* = 11.6, 4.4 Hz, 2H), 1.25 (d, *J* = 11.6 Hz, 2H).

^{13}C-NMR (100 MHz) δ 169.5 (CO), 132.3 (CH), 125.2 (C), 123.6 (CH), 122.1 (CH), 67.1 (CH_2), 37.8 (CH), 30.8 (C), 30.2 (CH_2), 22.7 (C).

IR ν_{max} 2949, 2927, 1755, 1652, 1234 cm^{-1}.

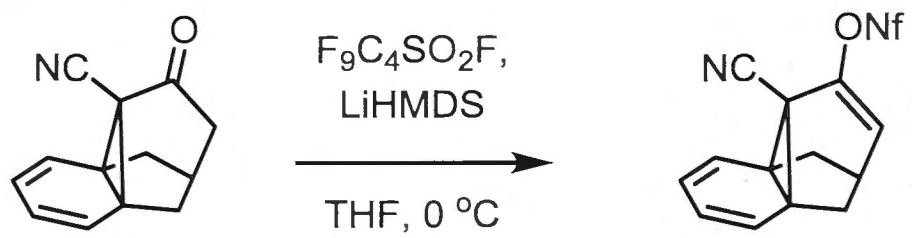
MS (EI, 70eV) *m/z* 212 ($M^{+\bullet}$, 90%), 197 (50), 183 (65), 167 (92), 155 (100), 115 (62).

HREIMS found: $M^{+\bullet}$, 212.0840. $C_{14}H_{12}O_2$ requires $M^{+\bullet}$, 212.0837.

mp 105-110 °C.

X-ray (see Appendix 1)

(2*s*,4a*r*,4b*R*,8a*S*)-4a-Cyano-2,4a-dihydro-1*H*-2,4b-methanocyclopropa[1,2:1,3]dibenzen-4-yl nonafluoromethanesulfonate (2.64)



2.37 **2.64**

A magnetically stirred solution of β-ketonitrile **2.37** (108 mg, 0.548 mmol) in THF (6 mL) maintained at 0 °C was treated with LiHMDS (1 M in THF, 0.82 mL, 0.821 mmol) and the resulting pale-orange solution stirred for 1 h. Perfluoro-1-butanesulfonyl fluoride (145 μL, 0.821 mmol) was then added and the ensuing mixture allowed to warm to room temperature. After 17 h the reaction mixture was quenched with $NaHCO_3$ (5 mL of a sat. aq. solution) then diluted with diethyl ether (5 mL) and brine (5 mL). The separated aqueous phase was extracted with diethyl ether (3 x 5 mL) and the combined organic layers washed with brine (1 x 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an

orange solid. Subjection of this material to flash column chromatography (silica, 7:3 - 2:8 v/v PS 30-40/diethyl ether gradient elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.7 in 13:7 v/v hexane/ethyl acetate) yielded the *title enol nonaflate* ***2.64*** as a pale-yellow foam (249 mg, 98% brsm).

Compound 2.64

^{1}H-NMR (400 MHz) δ 6.33 (dd, *J* = 7.3, 2.6 Hz, 2H), 6.06 (dd, *J* = 7.3, 2.6 Hz, 2H), 6.05 (d, *J* = 8.1 Hz, 1H), 2.67 (m, 1H), 1.87 (dd, *J* = 12.5, 4.9 Hz, 2H), 1.55 (d, *J* = 12.5 Hz, 2H).

^{13}C-NMR (100 MHz) δ 137.6 (C), 127.1 (CH), 121.0 (CH), 114.8 (CH), 111.9 (CN), 42.9 (C), 31.7 (CH), 26.7 (CH), 16.0 (C) (the signals due to the C_4F_9-group were not observed).

^{19}F-NMR (400 MHz) δ −80.69 (t, *J* = 9.8 Hz, 3F), −108.86 (m, 2F), −120.81 (m, 2F), −125.83 (m, 2F).

IR ν_{max} 2933, 2237, 1659, 1391, 1200, 1140 cm^{-1}.

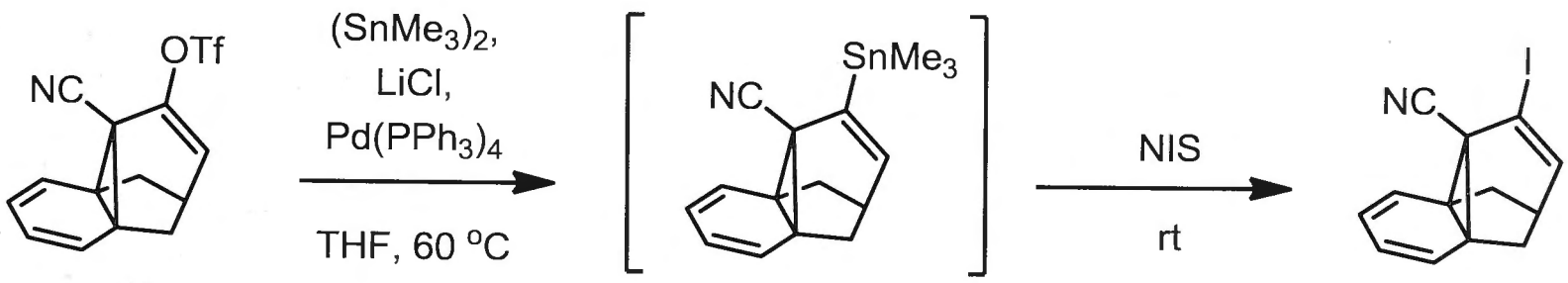
MS (EI, 70eV) *m/z* 479 ($M^{+\bullet}$, 35%), 196 (55), 168 (100), 141 (85), 115 (30), 69 (55).

HREIMS found: $M^{+\bullet}$, 479.0229. $C_{17}H_{10}F_9NO_3S$ requires $M^{+\bullet}$, 479.0238.

mp decomposition at 187 °C.

Concentration of fraction **B** (R_f = 0.2 in 13:7 v/v hexane/ethyl acetate) yielded compound **2.37** (5 mg, 4% recovery). This material was identical, in all respects, with an authentic sample.

(2*s*,4a*r*,4b*R*,8a*S*)-4-Iodo-2,4a-dihydro-1*H*-2,4b-methanocyclopropa[1,2:1,3]dibenzene-4a-carbonitrile (2.66)



2.61 **2.66**

A sealed tube was charged with enol triflate **2.61** (20 mg, 0.061 mmol), LiCl (15 mg, 0.36 mmol) and $Pd(PPh_3)_4$ (4 mg, 5 mol%) in degassed THF (3 mL) and the solution treated with hexamethylditin (20 mg, 13 µL, 0.061 mmol) that had been carefully melted prior to its addition. The tube was sealed and the contents heated at 60 °C for 14 h before being allowed to cool to room temperature. NIS (18 mg, 0.079 mmol) was then added to the ensuing mixture in one portion. The reaction mixture turned orange at this point and this colour change was accompanied by an exothermic reaction. Stirring was continued for 2 h and then the reaction mixture was concentrated with a stream of nitrogen. The residue was diluted with diethyl

ether (4 mL) and stirred with KF (4 mL of a 1 M aq. solution) for 22 h. The separated aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting yellow solid to flash column chromatography (silica, 8:2 v/v pentane/diethyl ether elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.7 in 13:7 v/v hexane/ethyl acetate) yielded the *title vinyl iodide* ***2.66*** (7 mg, 66% brsm) as colourless needles.

Compound 2.66

^{1}H-NMR (400 MHz) δ 6.69 (d, *J* = 7.7 Hz, 1H), 6.26 (m, 2H), 6.03 (m, 2H), 2.42 (m, 1H), 1.84 (dd, *J* = 12.4, 4.9 Hz, 2H), 1.57 (d, *J* = 12.4 Hz, 2H).

^{13}C-NMR (100 MHz) δ 138.0 (CH), 126.5 (CH), 121.7 (CH), 116.6 (CN), 79.7 (C), 43.8 (C), 32.2 (CH), 31.9 (CH_2), 23.0 (C).

IR ν_{max} 3040, 2965, 2931, 2858, 2232 cm^{-1}.

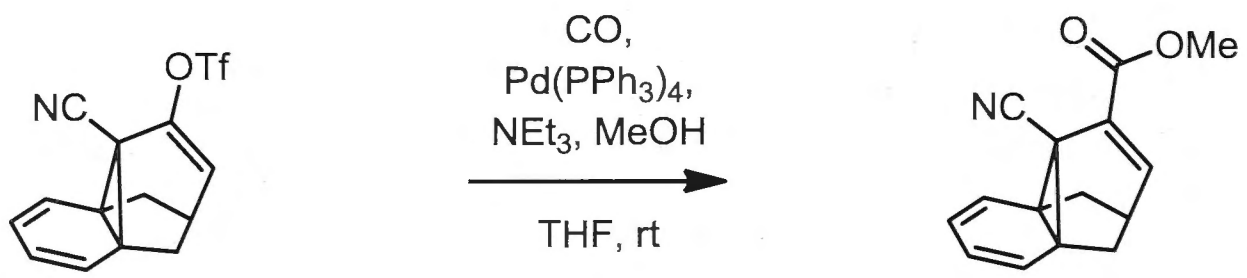
MS (EI, 70eV) *m/z* 307 ($M^{+\bullet}$, 50%), 180 (100), 153 (60), 115 (25).

HREIMS found: $M^{+\bullet}$, 306.9856. $C_{13}H_{10}IN$ requires $M^{+\bullet}$, 306.9858.

mp 148-153 °C.

Concentration of fraction **B** (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate) yielded compound **2.61** (9 mg, 43% recovery). This material was identical, in all respects, with an authentic sample.

Methyl (2*s*,4a*s*,4b*R*,8a*S*)-4a-Cyano-2,4a-dihydro-1*H*-2,4b-methanocyclopropa[1,2:1,3]di-benzene-4-carboxylate (2.68)



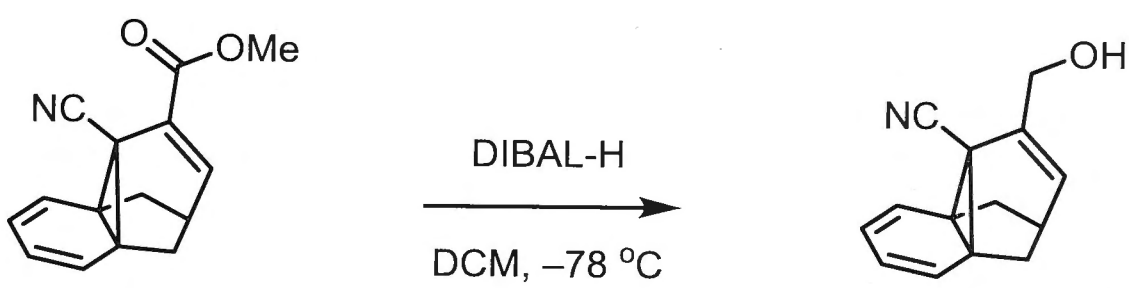
2.61 **2.68**

A magnetically stirred solution of enol triflate **2.61** (80 mg, 0.24 mmol) in methanol (0.79 mL, 19 mmol) was treated with $Pd(PPh_3)_4$ (28 mg, 0.024 mmol, 10 mol%) and triethylamine (135 µL, 0.972 mmol). The flask was evacuated and refilled with carbon monoxide three times before being stirred vigorously at room temperature for 3 h under an atmosphere of carbon monoxide. The flask was sparged with nitrogen to remove residual carbon monoxide and to concentrate the reaction mixture. Subjection of the crude material to flash column chromatography (silica, 1:1 v/v PS-30-40/diethyl ether elution) yielded, after concentration of

the appropriate fractions (R_f = 0.3 in 13:7 hexane/ethyl acetate), the *title methyl ester* ***2.68*** (5 mg, 93%) as a colourless, crystalline solid.

^{1}H-NMR (400 MHz) δ 7.10 (d, *J* = 7.7 Hz, 1H), 6.30 (dd, *J* = 7.3, 2.7 Hz, 2H), 5.98 (dd, *J* = 7.3, 2.7 Hz, 2H), 3.80 (s, 3H), 2.63 (m, 1H), 1.86 (dd, *J* = 12.3, 5.0 Hz, 2H), 1.41 (d, *J* = 12.3 Hz, 2H).
^{13}C-NMR (100 MHz) δ 164.9 (CO), 137.5 (CH), 126.8 (CH), 122.2 (C), 121.2 (CH), 121.1 (C), 114.4 (CN), 52.1 (CH_3), 41.9 (C), 30.9 (CH_2), 28.0 (CH), 12.9 (C).
IR ν_{max} 3041, 2996, 2927, 2849, 2232, 1724, 1619 cm^{-1}.
MS (EI, 70eV) *m/z* 239 ($M^{+\bullet}$, 30%), 224 (15), 205 (30), 180 (100), 153 (40), 115 (20).
HREIMS found: $M^{+\bullet}$, 239.0946. $C_{15}H_{13}NO_2$ requires $M^{+\bullet}$, 239.0946.
mp 127-130 °C.

(2*s*,4a*s*,4b*R*,8a*S*)-4-(Hydroxymethyl)-2,4a-dihydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzene-4a-carbonitrile (2.69)



2.68 **2.69**

A magnetically stirred solution of methyl ester **2.68** (15 mg, 0.060 mmol) in DCM (0.6 ml) maintained at −78 °C was slowly treated with DIBAL-H (88 µL, 0.130 mmol, 1.5 M solution in toluene). After 2 h ethyl acetate (0.5 mL) was added, the reaction mixture allowed to warm to room temperature, treated with Rochelle salt (5 mL) and stirred vigorously for 1 h. The separated aqueous layer was extracted with diethyl ether (2 x 10 mL) and the combined organic layers washed with brine (1 x 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting yellow oil to flash column chromatography (silica, 3:7 v/v pentane/diethyl ether elution) yielded, after concentration of the appropriate fractions (R_f = 0.2 in 13:7 v/v hexane/ethyl acetate), the *title alcohol* ***2.70*** (8 mg, 75%) as a pale-yellow solid.

^{1}H-NMR (400 MHz) δ 6.26 (dd, *J* = 7.4, 2.6 Hz, 2H), 6.12 (d, *J* = 7.4 Hz, 1H), 6.03 (dd, *J* = 7.4, 2.6 Hz, 2H), 4.36 (d, *J* = 1.0 Hz, 2H), 2.49 (m, 1H), 1.78 (dd, *J* = 12.1, 4.9 Hz, 2H) 1.43 (d, *J* = 12.1 Hz, 2H).
^{13}C-NMR (100 MHz) δ 128.2 (C), 125.9 (CH), 124.1 (CH), 122.3 (CH), 115.8 (CN), 64.0 (CH_2), 41.9 (C), 32.1 (CH_2), 27.8 (CH), 14.3 (C).

IR ν_{max} 3453, 2927, 2231, 1724, 1433 cm^{-1}.

MS (EI, 70eV) *m/z* 211 ($M^{+\bullet}$, 30%), 180 (100), 153 (40), 115 (30), 69 (50).

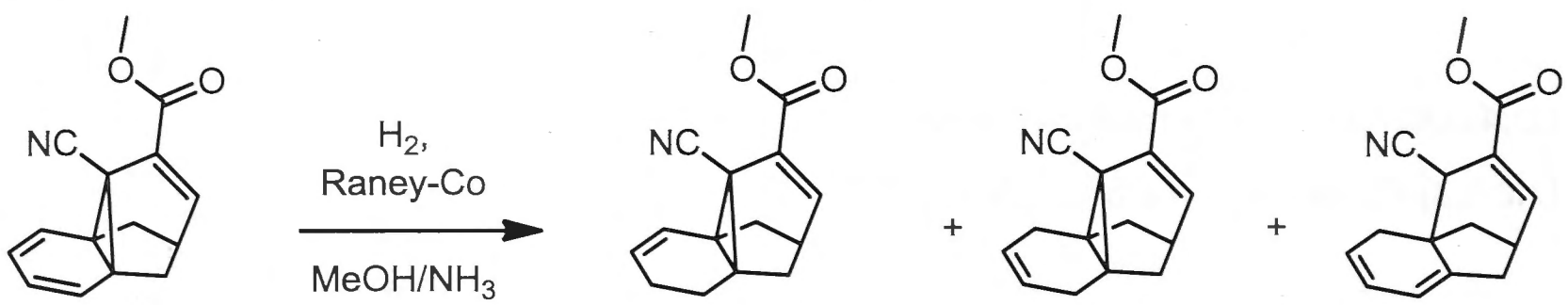
HREIMS found: $M^{+\bullet}$, 211.1000. $C_{14}H_{13}NO$ requires $M^{+\bullet}$, 211.0997.

mp 118-123 °C.

Methyl (2*SR*,4a*SR*,4b*RS*,8a*RS*)-4a-Cyano-2,4a,5,6-tetrahydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzene-4-carboxylate (2.70),

Methyl (2*r*,4a*r*,4b*R*,8a*S*)-4a-Cyano-2,4a,5,8-tetrahydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzene-4-carboxylate (2.71) and

Methyl (6*SR*,9a*RS*)-9-Cyano-1,5,6,9-tetrahydro-6,9a-methanobenzo[7]annulene-8-carboxylate (2.72)



2.68 **2.70** **2.71** **2.72**

A magnetically stirred solution of methyl ester **2.68** (40 mg, 0.17 mmol) in $MeOH/NH_3$ (2 mL) was treated (using a magnetised spatula) with a spatula tip (200 mol%) of Raney-Cobalt slurry in $MeOH/H_2O$ maintained under constant N_2 flow. The flask was then evacuated and refilled with hydrogen gas three times and the reaction mixture stirred vigorously in order to suspend the magnetic Raney-cobalt particles. After 4 h at room temperature the flask was sparged with nitrogen and the reaction mixture filtered through Celite™ and the filtrate concentrated under reduced pressure. Subjection of the resulting oil to flash column chromatography (silica, 7:3 v/v pentane/diethyl ether elution) yielded three fractions, A, B and C.

Concentration of fraction **A** (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate) yielded the *title ring-opened ester* ***2.72*** (2 mg, 5%) as a pale-yellow, crystalline solid.

Compound 2.72

^{1}H-NMR (400 MHz) δ 7.35 (d, *J* = 6.7 Hz, 1H), 6.06 (m, 1H), 5.89 (m, 1H), 5.78 (m, 1H), 3.76 (s, 3H), 3.69 (s, 1H), 2.90 (dd, *J* = 11.9, 6.5 Hz, 1H), 2.87 (m, 1H), 2.60 (dd, *J* = 17.0, 6.5 Hz, 1H), 2.46 (d, *J* = 17.0 Hz, 1H), 2.26 (d, *J* = 17.0 Hz, 1H), 2.16 (d, *J* = 2.2 Hz, 1H), 1.60 (dd, *J* = 11.9, 3.8 Hz, 1H).

^{13}C-NMR (100 MHz) δ 165.4 (CO), 147.8 (CH), 143.0 (C), 126.0 (CH), 124.1 (C), 122.4 (CH), 120.1, (CH), 118.6 (CN), 52.1 (CH_3), 41.6 (C), 39.1 (2 x CH_2), 35.0 (CH), 34.1 (CH), 32.7 (CH_2).

IR ν_{max} 3041, 2951, 2867, 2233, 1718, 1644 cm^{-1}.

MS (EI, 70eV) *m/z* 241 ($M^{+\bullet}$, 40%), 182 (50), 117 (80), 91 (100).

HREIMS found: $M^{+\bullet}$, 241.1102. $C_{15}H_{15}NO_2$ requires $M^{+\bullet}$, 241.1103.

mp 134-144 °C.

X-ray (see Appendix 3).

Concentration of fraction **B** (R_f = 0.5 in 13:7 v/v hexane/ethyl acetate) yielded the *title asymmetrically hydrogenated ester* ***2.70*** (15 mg, 37%) as a colourless, crystalline solid.

Compound 2.70

^{1}H-NMR (400 MHz) δ 7.06 (d, *J* = 7.7 Hz, 1H), 6.09 (dt, *J* = 9.9, 3.6 Hz, 1H), 5.95 (d, *J* = 9.9 Hz, 1H), 3.78 (s, 3H), 2.76 (m, 1H), 2.35 (m, 1H), 2.23 (m, 1H), 2.18 (m, 1H), 2.12 (m, 1H), 1.74 (dd, *J* = 5.0, 4.3 Hz, 2H), 1.71 (dd, *J* = 5.0, 4.3 Hz, 2H), 1.21 (dd, *J* = 8.1, 4.3 Hz, 2H).

^{13}C-NMR (100 MHz) δ 165.0 (CO), 140.2 (CH), 139.8 (C), 132.4 (CH), 121.6 (CH), 117.6 (CN), 52.0, (CH_3), 33.8 (CH_2), 33.7 (C), 33.6 (C), 31.6 (CH), 30.8 (CH_2), 29.5 (C), 22.4 (CH_2), 20.2 (CH_2).

IR ν_{max} 3031, 2927, 2850, 2230, 1716, 1616 cm^{-1}.

MS (EI, 70eV) *m/z* 241 ($M^{+\bullet}$, 65%), 226 (100), 209 (35), 182 (70), 115 (35).

HREIMS found: $M^{+\bullet}$, 241.1103. $C_{15}H_{15}NO_2$ requires $M^{+\bullet}$, 241.1103.

mp 130-134 °C.

Concentration of fraction **C** (R_f = 0.4 in 13:7 v/v hexane/ethyl acetate) yielded the *title symmetrically hydrogenated ester* ***2.71*** (10 mg, 25%) as a colourless, crystalline solid.

Compound 2.71

^{1}H-NMR (400 MHz) δ 7.06 (d, *J* = 7.7 Hz, 1H), 5.75 (s, 2H), 3.79 (s, 3H), 2.70 (m, 1H), 2.59 (s, 4H), 1.72 (dd, *J* = 12.0, 4.9 Hz, 2H), 1.25 (d, *J* = 12.0 Hz, 2H).

^{13}C-NMR (100 MHz) δ 165.1 (CO), 139.8 (CH), 124.0 (C), 123.2 (CH_2), 116.5 (CN), 52.0 (CH_3), 34.1 (CH_2), 31.6 (C), 31.2 (CH), 23.8 (CH_2), 23.6 (C).

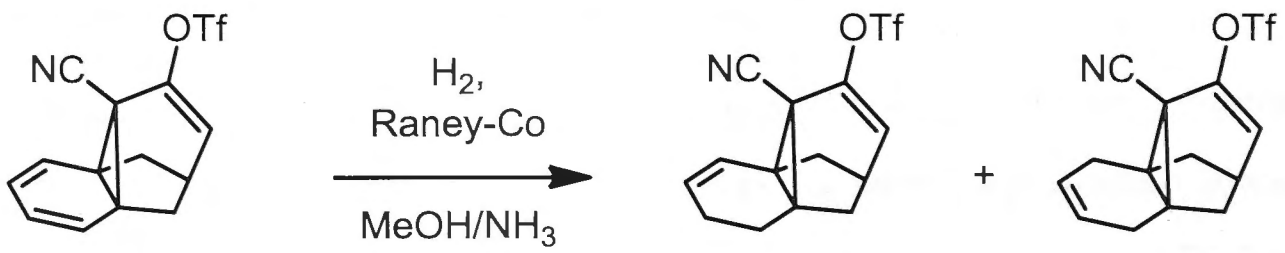
IR ν_{max} 3035, 2995, 2923, 2229, 1724, 1618, 1269 cm^{-1}.

MS (EI, 70eV) *m/z* 241 ($M^{+\bullet}$, 100%), 226 (50), 208 (60), 180 (55), 115 (35), 67 (50).

HREIMS found: $M^{+\bullet}$, 241.1101. $C_{15}H_{15}NO_2$ requires $M^{+\bullet}$, 241.1103.

mp 150-154 °C.

(2*SR*,4a*RS*,4b*RS*,8a*RS*)-4a-Cyano-2,4a,5,6-tetrahydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzen-4-yl trifluoromethanesulfonate (2.73) and (2*r*,4a*s*,4b*R*,8a*S*)-4a-Cyano-2,4a,5,8-tetrahydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzen-4-yl trifluoromethanesulfonate (2.74)



2.61 **2.73** **2.74**

A magnetically stirred solution of enol triflate **2.61** (100 mg, 0.304 mmol) in MeOH/NH_3 (4 mL) was treated (using a magnetised spatula) with a spatula tip (*ca*. 200 mol%) of Raney-Cobalt slurry in MeOH/H_2O maintained under constant nitrogen flow. The flask was evacuated and refilled with hydrogen gas three times and the reaction mixture stirred very vigorously to suspend the magnetic Raney-cobalt particles. After 1.5 h at room temperature the flask was sparged with nitrogen and the reaction mixture filtered through Celite™ and the filtrate concentrated under reduced pressure. Subjection of the resulting pale-yellow oil to flash column chromatography (silica, 3:1 v/v pentane/diethyl ether elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate) yielded the *title asymmetrically hydrogenated enol triflate* ***2.73*** (24 mg, 24%) as a colourless, crystalline solid.

Compound 2.73

^{1}H-NMR (400 MHz) δ 6.11 (dt, *J* = 9.5, 3.8 Hz, 1H), 6.02 (m, 1H), 6.00 (d, *J* = 8.3 Hz, 1H), 2.80 (m, 1H), 2.39 (m, 1H), 2.25 (m, 1H), 2.24 (m, 1H), 2.09 (m, 1H), 1.78 (dd, *J* = 12.9, 5.0 Hz, 1H), 1.69 (dd, *J* = 12.9, 5.0 Hz, 1H), 1.36 (d, *J* = 5.0 Hz, 1H), 1.33 (d, *J* = 5.0 Hz, 1H).

^{13}C-NMR (100 MHz) δ 139.3 (C), 132.4 (CH), 120.8 (CH), 120.1 (C), 117.0 (CH), 114.7 (CN), 35.7 (C), 35.2 (C), 34.8 (CH_2), 31.6 (CH_2), 29.7 (CH), 22.2 (CH_2), 19.4 (CH_2).

IR ν_{max} 2932, 2859, 2237, 1655, 1425 cm^{-1}.

MS (EI, 70eV) *m/z* 331 ($M^{+\bullet}$, 75%), 198 (100), 170 (50), 115 (40), 69 (35).

HREIMS found: $M^{+\bullet}$, 331.0497. $C_{14}H_{12}F_3NO_3S$ requires $M^{+\bullet}$, 331.0490.

mp 155-160 °C.

Concentration of fraction **B** (R_f = 0.5 in 13:7 v/v hexane/ethyl acetate) yielded the *title asymmetrically hydrogenated enol triflate* ***2.74*** (16 mg, 16%) as a clear, colourless oil.

Compound 2.74

^{1}H-NMR (400 MHz) δ 5.99 (d, *J* = 8.3 Hz, 1H), 5.74 (s, 2H), 2.74 (m, 1H), 2.63 (m, 4H), 1.73 (dd, *J* = 12.2, 4.9 Hz, 2H), 1.37 (d, *J* = 12.2 Hz, 2H).

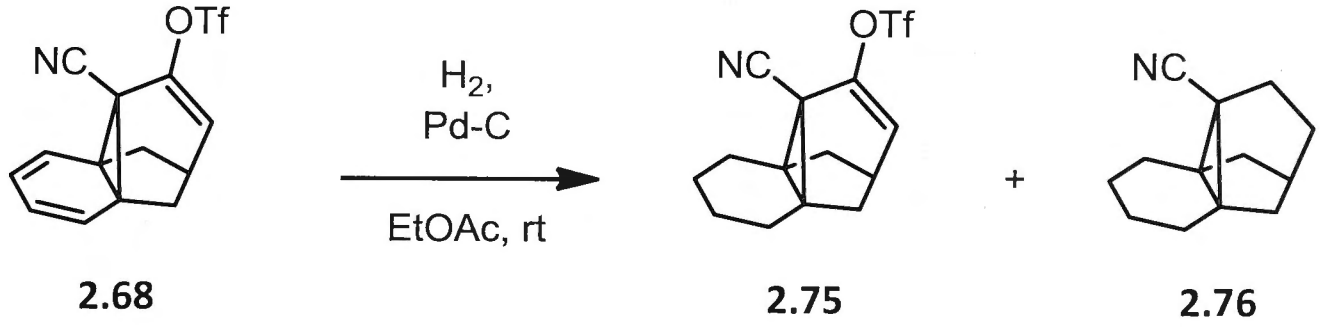
^{13}C-NMR (100 MHz) δ 139.3 (C), 127.5 (C), 123.2 (CH), 118.5 (q, *J* = 321 Hz, CF_3), 116.7 (CH), 113.8 (CN), 34.7 (CH_2), 33.6 (C), 29.0 (CH), 23.6 (CH_2).

IR ν_{max} 2930, 2901, 2845, 2238, 1658, 1425 cm^{-1}.

MS (EI, 70eV) *m/z* 331 ($M^{+\bullet}$, 75%), 279 (30), 198 (85), 115 (50), 67 (100).

HREIMS found: $M^{+\bullet}$, 331.0486. $C_{14}H_{12}F_3NO_3S$ requires $M^{+\bullet}$, 331.0490.

(2*r*,4a*s*,4b*R*,8a*S*)-4a-Cyano-2,4a,5,6,7,8-hexahydro-1*H*-2,4b-methanocyclopropa[1,2:1,3]-dibenzen-4-yl trifluoromethanesulfonate (2.75) and (2*r*,4a*r*,4b*R*,8a*S*)-Octahydro-4a*H*-2,4b-methanocyclopropa[1,2:1,3]dibenzene-4a-carbonitrile (2.76)



2.68 **2.75** **2.76**

A magnetically stirred solution of enol triflate **2.61** (100 mg, 0.304 mmol) in ethyl acetate (3 mL) was treated with palladium on charcoal (16 mg, 5 mol%) and the flask evacuated and refilled with hydrogen three times. The reaction mixture was stirred vigorously at room temperature for 0.5 h, then sparged with nitrogen to remove excess hydrogen gas, filtered through Celite™ and the filtrate concentrated under reduced pressure. Subjection of the resulting oil to flash column chromatography (silica, 3:1 v/v pentane/diethyl ether elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.7 in 13:7 v/v hexane/ethyl acetate) yielded the *title bis-hydrogenated enol triflate* ***2.75*** (10 mg, 10%) as a clear, colourless oil.

Compound 2.75

^{1}H-NMR (400 MHz) δ 5.93 (d, *J* = 8.3 Hz, 1H), 2.66 (m, 1H), 2.06 (m, 2H), 1.68 (dd, *J* = 12.7, 4.9 Hz, 2H), 1.66 (m, 2H), 1.38 (m, 2H), 1.29 (d, *J* = 12.7 Hz, 2H).

^{13}C-NMR (100 MHz) δ 139.5 (C), 116.2 (CH), 115.5 (CN), 35.7 (CH_2), 34.8 (C), 29.4 (CH), 25.7 (C), 22.5 (CH_2), 21.0 (CH_2).

IR ν_{max} 2941, 2859, 2236, 1658, 1599, 1426, 1210 cm^{-1}.

MS (EI, 70eV) *m/z* 333 ($M^{+\bullet}$, 25%), 200 (100), 116 (15), 69 (30).

HREIMS found: $M^{+\bullet}$, 333.0642. $C_{14}H_{14}F_3NO_3S$ requires $M^{+\bullet}$, 333.0647.

Concentration of fraction **B** (R_f = 0.9 in 13:7 v/v hexane/ethyl acetate) yielded the *title fully hydrogenated nitrile* ***2.76*** (35 mg, 34%) as a clear, colourless oil.

Compound 2.76

^{1}H-NMR (400 MHz) δ 2.09 (m, 2H), 1.93 (m, 1H), 1.89 (m, 2H), 1.78 (m, 2H), 1.71 (m, 2H), 1.46 (m, 2H), 1.38 (m, 2H), 1.26 (m, 2H).

^{13}C-NMR (100 MHz) δ 121.9 (CN), 38.7 (CH_2), 32.3 (C), 30.4 (CH), 25.9 (CH_2), 25.6 (CH_2), 21.1 (CH_2), 20.2 (CH_2).

IR ν_{max} 2942, 2858, 2218, 1717, 1642, 1445 cm^{-1}.

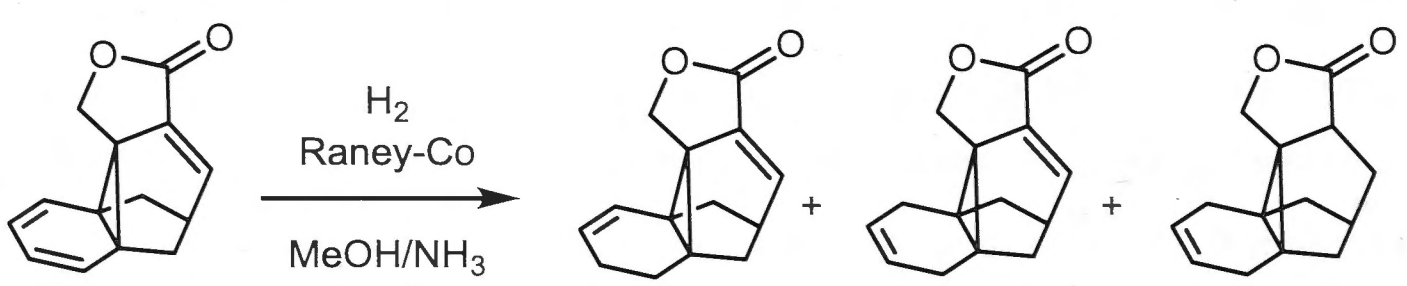
MS (EI, 70eV) *m/z* 187 ($M^{+\bullet}$, 75%), 116 (55), 84 (100), 67 (50).

HREIMS found: $M^{+\bullet}$, 187.1361. $C_{13}H_{17}N$ requires $M^{+\bullet}$, 187.1361.

(5*SR*,6a*RS*,10a*RS*,10b*SR*)-5,6,7,8-Tetrahydro-5,10a-methanobenzo[2,3]cyclopropa[1,2-*d*]isobenzofuran-3(1*H*)-one (2.77),

(5*r*,6a*R*,10a*S*,10b*r*)-5,6,7,10-Tetrahydro-5,10a-methanobenzo[2,3]cyclopropa[1,2-*d*]isobenzofuran-3(1*H*)-one (2.78) and

(5*s*,6a*R*,10a*S*,10b*s*)-3a,4,5,6,7,10-Hexahydro-5,10a-methanobenzo[2,3]cyclopropa[1,2-*d*]isobenzofuran-3(1*H*)-one (2.79)



A magnetically stirred solution of lactone **1.13** (15 mg, 0.072 mmol) in ammoniacal MeOH (1 mL) maintained under constant N_2 flow was treated (using a magnetised spatula) with a spatula tip (ca. 200 mol%) of Raney-Cobalt slurry in MeOH/H_2O. The sealed flask was evacuated and refilled with hydrogen gas three times and the resulting mixture stirred vigorously (to distribute the magnetic cobalt particles in the reaction mixture) at room temperature for 3.5 h. The flask was then flushed with nitrogen, the reaction mixture filtered through Celite™ and the filtrate concentrated under reduced pressure. The resulting oil was subjected to flash column chromatography (silica, 4:1 v/v pentane/diethyl ether elution) to give, after concentration of the appropriate fractions, three compounds, A, B and C.

Concentration of fraction **A** (R_f = 0.7 (0.68) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.79*** (1 mg, 5%) as a colourless, crystalline solid.

Compound 2.79

^{1}H-NMR (400 MHz) δ 5.57 (d, *J* = 2.4 Hz, 2H), 4.02 (dd, *J* = 10.4, 0.8 Hz, 1H), 3.98 (d, *J* = 10.4 Hz, 1H), 2.89 (dd, *J* = 11.6, 7.9 Hz, 1H), 2.45 - 2.05 (complex m, 4H), 1.90 - 1.51 (complex m, 7H).

^{13}C-NMR (100 MHz) δ 178.6 (C), 124.6 (CH), 124.5 (CH), 67.7 (CH2), 39.3 (CH_2), 36.8 (CH2), 35.9 (CH), 29.8 (C), 29.7 (CH), 27.9 (CH_2), 26.6 (CH_2), 26.3 (C), 25.8 (C), 25.5 (CH_2).

IR ν_{max} 2851, 1778, 1436, 1365, 1189, 1152, 1078, 1032 cm^{-1}.

MS (EI, 70eV) *m/z* 216 ($M^{+\bullet}$, 100%), 202 (8), 185 (9), 174 (12), 158 (22), 143 (28), 129 (42), 117 (42), 91 (75).

HREIMS found: $M^{+\bullet}$, 216.1149. $C_{14}H_{16}O_2$ requires $M^{+\bullet}$, 216.1150.

mp 95-99 °C.

Concentration of fraction **B** (R_f = 0.6 (0.61) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.77*** (8 mg, 50%) as a colourless, crystalline solid.

Compound 2.77

^{1}H-NMR (400 MHz) δ 6.99 (d, *J* = 9.6 Hz, 1H), 5.97 (m, 1H), 5.82 (m, 1H), 4.41 (d, *J* = 12.8 Hz, 1H), 4.13 (d, *J* = 12.8 Hz, 1H), 2.94 (m, 1H), 2.27 (m, 1H), 1.99 (m, 1H), 1.90 - 1.40 (complex m, 4H), 1.00 (m, 2H).

^{13}C-NMR (100 MHz) δ 169.6 (C), 134.7 (CH), 126.7 (CH), 126.5 (C), 124.2 (CH), 67.6 (CH_2), 38.4 (C), 33.7 (CH), 33.4 (CH_2), 30.2 (CH_2), 28.8 (C), 28.0 (C), 22.9 (CH_2), 18.9 (CH_2).

IR ν_{max} 2926, 2854, 1758, 1653, 1436, 1359, 1239, 1052, 1020 cm^{-1}.

MS (EI, 70eV) *m/z* 214 ($M^{+\bullet}$, 100%), 199 (10), 186 (32), 169 (22), 155 (26), 141 (28), 128 (30), 115 (31), 91 (31).

HREIMS found: $M^{+\bullet}$, 214.0993. $C_{14}H_{14}O_2$ requires $M^{+\bullet}$, 214.0994.

mp 106-110 °C.

Concentration of fraction **C** (R_f = 0.6 (0.59) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.78*** (6 mg, 40%) as a colourless, crystalline solid.

Compound 2.78

^{1}H-NMR (400 MHz) δ 6.93 (d, *J* = 6.8 Hz, 1H), 5.66 (m, 2H), 4.09 (s, 2H), 2.87 (m, 1H), 2.56 (d, *J* = 16.8 Hz, 2H), 2.30 (m, 2H), 1.66 (dd, *J* = 11.6, 4.8 Hz, 2H), 0.96 (d, *J* = 11.6 Hz, 2H).

^{13}C-NMR (100 MHz) δ 169.7 (C), 133.7 (CH), 126.3 (C), 124.6 (CH), 67.1 (CH_2), 32.9 (CH_2), 32.7 (CH), 31.6 (C), 25.3 (C), 23.6 (CH_2).

IR ν_{max} 2923, 1756, 1652, 1431, 1239, 1146, 1084, 1052 cm^{-1}.

MS (EI, 70eV) *m/z* 214 ($M^{+\bullet}$, 100%), 199 (22), 185 (40), 171 (22), 155 (29), 141 (38), 129 (59), 115 (57), 91 (67).

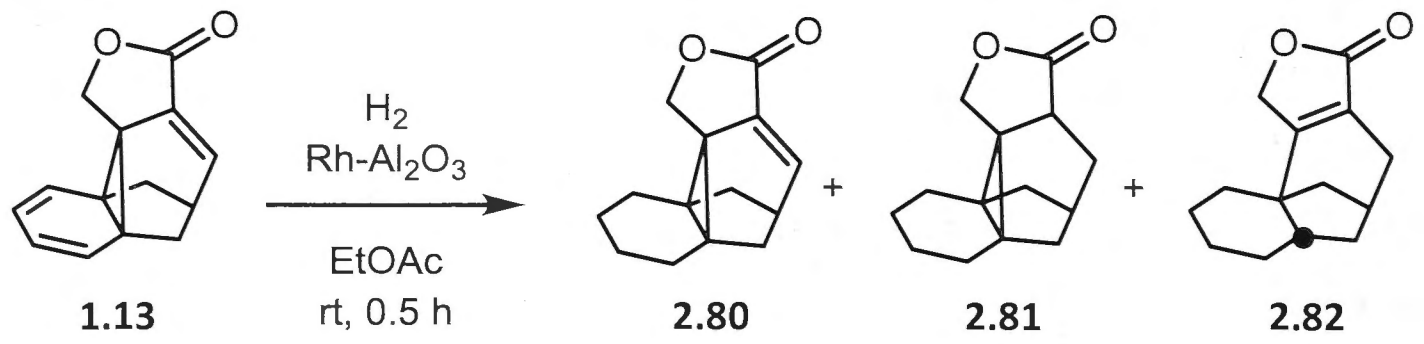
HREIMS found: $M^{+\bullet}$, 214.0992. $C_{14}H_{14}O_2$ requires $M^{+\bullet}$, 214.0994.

mp 138-140 °C.

(5*r*,6a*R*,10a*S*,10b*r*)-5,6,7,8,9,10-Hexahydro-5,10a-methanobenzo[2,3]cyclopropa[1,2-*d*]isobenzofuran-3(1*H*)-one (2.80),

(5*r*,6a*R*,10a*S*,10b*r*)-Octahydro-5,10a-methanobenzo[2,3]cyclo-propa[1,2-d]isobenzofuran-3(1*H*)-one (2.81) and

(5*SR*,10a*SR*)-4,5,6,6a,7,8,9,10-Octahydro-5,10a-methanobenzo[3,4]cyclohepta[1,2-*c*]furan-3(1*H*)-one (2.82)



1.13 **2.80** **2.81** **2.82**

A magnetically stirred solution of lactone **1.13** (12 mg, 0.056 mmol) in ethyl acetate (2 mL) was treated with 5% rhodium on alumina (3 mg, 3 mol%). The sealed flask was then evacuated and refilled with hydrogen gas three times and stirred vigorously at room temperature for 0.5 h. The flask was then flushed with nitrogen and the reaction mixture filtered through Celite™ and concentrated under reduced pressure. The resulting colourless oil was subjected to flash column chromatography (silica, 4:1 v/v pentane/diethyl ether elution) to give, after concentration of the appropriate fractions, three compounds, A, B and C.

Concentration of fraction **A** (R_f = 0.7 (0.68) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.81*** (6 mg, 50%) as a colourless, crystalline solid.

Compound 2.81

^{1}H-NMR (400 MHz) δ 4.29 (d, *J* = 9.2 Hz, 1H), 4.17 (dd, *J* = 9.2, 1.2 Hz, 1H), 2.86 (dd, *J* = 11.6, 8.0 Hz, 1H), 2.04 (m, 1H), 1.80 - 1.05 (complex m, 13H), 0.78 (m, 1H).

^{13}C-NMR (100 MHz) δ 178.6 (C), 67.7 (CH_2), 40.5 (CH_2), 37.8 (CH_2), 36.4 (CH), 30.8 (C), 30.1 (CH), 27.6 (CH_2), 26.4 (C), 25.8 (C), 25.0 (CH_2), 24.2 (CH_2), 22.2 (CH_2), 21.5 (CH_2).

IR ν_{max} 2924, 2850, 1769, 1667 cm^{-1}.

MS (EI, 70eV) *m/z* 218 ($M^{+\bullet}$, 70%), 189 (15), 121 (100), 91 (30).

HREIMS found: $M^{+\bullet}$, 218.1307. $C_{14}H_{18}O_2$ requires $M^{+\bullet}$, 218.1307.

mp 85-89 °C.

Concentration of fraction **B** (R_f = 0.6(0) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.80*** (3 mg, 25%) as a colourless, crystalline solid.

Compound 2.80

^{1}H-NMR (400 MHz) δ 6.92 (d, *J* = 7.2 Hz, 1H), 4.37 (s, 2H), 2.78 (m, 1H), 1.93 (m, 2H), 1.75 - 0.80 (complex m, 10 H).

^{13}C-NMR (100 MHz) δ 169.8 (C), 133.7 (CH), 126.3 (C), 66.7 (CH_2), 34.2 (CH_2), 33.1 (CH), 31.6 (C), 24.5 (C), 22.0 (CH_2), 21.9 (CH_2).

IR ν_{max} 2929, 2853, 1761, 1657, 1450, 1364, 1235, 1072, 1056, 1038 cm^{-1}.

MS (ESI, +ve) *m/z* 239 ($[M+Na]^+$, 97%), 217 ($[M+H]^+$, 100).

HRESIMS found: $[M+H]^+$ 217.1231. $C_{14}H_{17}O_2$ requires $[M+H]^+$, 217.1229.

mp 85-90 °C.

Concentration of fraction **C** (R_f = 0.6 (0.57) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.82*** (1 mg, 8%) as a colourless, crystalline solid.

Compound 2.82

^{1}H-NMR (400 MHz) δ 4.75 (m, 2H), 2.58 (m, 1H), 2.40 (m, 1H), 2.24 (dd, *J* = 11.6, 6.0 Hz, 1H), 2.08 (m, 1H), 2.00 - 1.80 (complex m, 2H), 1.75 - 1.05 (complex m, 10H).

^{13}C-NMR (100 MHz) δ 174.8 (C), 172.3 (C), 123.2 (C), 69.1 (CH_2), 46.4 (CH), 44.1 (C), 38.7 (CH_2), 35.3 (CH_2), 32.5 (CH_2), 32.0 (CH), 31.7 (CH_2), 28.5 (CH_2), 25.5 (CH_2), 20.9 (CH_2).

IR ν_{max} 2924, 2850, 1769, 1667, 1432, 1383, 1342, 1299, 1195, 1046, 1018 cm^{-1}.

MS (EI, 70eV) *m/z* 218 ($M^{+\bullet}$, 100%), 145 (20), 131 (25), 117 (20), 91 (45).

HREIMS found: $M^{+\bullet}$, 218.1312. $C_{14}H_{18}O_2$ requires $M^{+\bullet}$, 218.1307.

mp 44-46 °C.

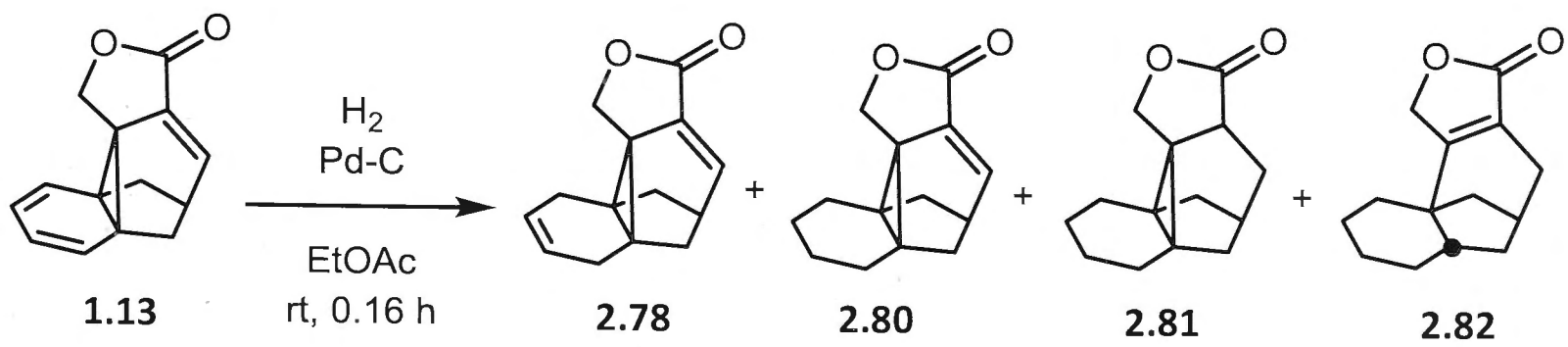
X-ray (see Appendix 4).

(5*r*,6a*R*,10a*S*,10b*r*)-5,6,7,10-Tetrahydro-5,10a-methanoben-zo[2,3]cyclopropa[1,2-*d*]isobenzofuran-3(1*H*)-one (2.78),

(5*r*,6a*R*,10a*S*,10b*r*)-5,6,7,8,9,10-Hexahydro-5,10a-methanobenzo[2,3]cyclopropa[1,2-*d*]iso-benzofuran-3(1*H*)-one (2.80),

(5*r*,6a*R*,10a*S*,10b*r*)-Octahydro-5,10a-methanobenzo[2,3]cyclo-propa[1,2-d]isobenzofuran-3(1*H*)-one (2.81) and

(5*SR*,10a*SR*)-4,5,6,6a,7,8,9,10-Octahydro-5,10a-methanobenzo[3,4]cyclohepta[1,2-*c*]furan-3(1*H*)-one (2.82)



A magnetically stirred solution of lactone **1.13** (12 mg, 0.056 mmol) in ethyl acetate (2 mL) was treated with 10% palladium on carbon (7 mg, 11 mol%). The sealed flask was evacuated and

refilled with hydrogen gas three times. After 0.16 h of vigorous stirring at room temperature the flask was flushed with nitrogen, the reaction mixture filtered through Celite™ and the filtrate concentrated under reduced pressure. The resulting oil was subjected to flash column chromatography (silica, 4:1 v/v pentane/diethyl ether elution) to give, after concentration of the appropriate fractions, four compounds, A, B, C and D.

Concentration of fraction **A** (R_f = 0.7 (0.68) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.81*** (2 mg, 16%) as a colourless, crystalline solid. This material was identical, in all respects, with an authentic sample.

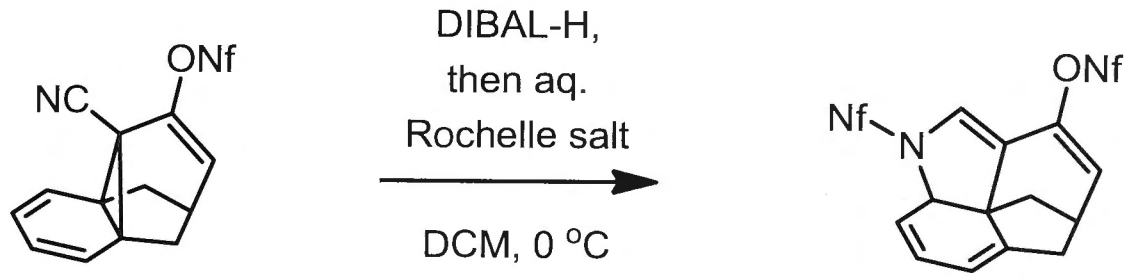
Concentration of fraction **B** (R_f = 0.6(0) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.80*** (1 mg, 8%) as a colourless, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **C** (R_f = 0.6 (0.59) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.78*** (5 mg, 42%) as a colourless, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **D** (R_f = 0.6 (0.57) in 13:7 v/v hexane/ethyl acetate) gave the *title compound* ***2.82*** (4 mg, 33%) as a colourless, crystalline solid. This material was identical, in all respects, with an authentic sample.

6.3. Experimental Procedures for Chapter 3

(2a*RS*,2a1*RS*,7*SR*)-2-([Nonafluoromethyl]sulfonyl)-2,2a,6,7-tetrahydro-2a1,7-methanocyclo-hepta[*cd*]indol-9-yl nonafluoromethanesulfonate, (Nonafluoro aza[5.6.5.6]fenestratetraene, 3.48)



2.64 **3.48**

While protected from light, a magnetically stirred solution of enol nonaflate **2.64** (100 mg, 0.21 mmol) in DCM (4 mL) at 0 °C was slowly treated with DIBAL-H (0.21 mL, 0.31 mmol, 1.5 M solution in toluene) and stirring continued for 20 h. The reaction mixture was quenched by adding ethyl acetate (1 mL) then allowed to warm to room temperature and subsequently treated with Rochelle salt (5 mL). After the mixture had been stirred vigorously for 2 h, it was extracted with DCM (3 x 5 mL), washed with water (1 x 5 mL), dried ($MgSO_4$) and filtered. Flash column chromatography of the resulting brown oil (silica, 7:3 v/v PS 30-40/diethyl ether elution) gave, after concentration of the appropriate fractions (R_f = 0.7 in 13:7 v/v hexane/ethyl acetate), the *title compound* ***3.48*** as colourless crystals (49 mg, 31%) which turned brown within minutes.

^{1}H-NMR (400 MHz) δ 6.32 (s, 1H), 6.05 (d, *J* = 7.4 Hz, 1H), 6.01 (dd, *J* = 9.4, 5.9 Hz, 1H), 5.79 (m, 1H), 5.58 (dd, *J* = 9.4, 3.3 Hz, 1H), 5.43 (s, 1H), 2.88 (m, 1H), 2.65 (m, 2H), 2.19 (d, *J* = 10.6 Hz, 2H), 1.94 (dd, *J* = 10.6, 4.0 Hz, 2H).

^{13}C-NMR (100 MHz) δ 140.6 (C), 124.8 (CH), 124.4 (CH), 119.8 (CH), 117.9 (CH), 66.5 (CH), 56.0 (C), 42.7 (CH_2), 37.6 (CH_2), 33.1 (CH) (the signals due to the two CF_3-groups were not observed).

IR ν_{max} 3436, 3115, 2928, 2855, 2225, 1668, 1610, 1411 cm^{-1}.

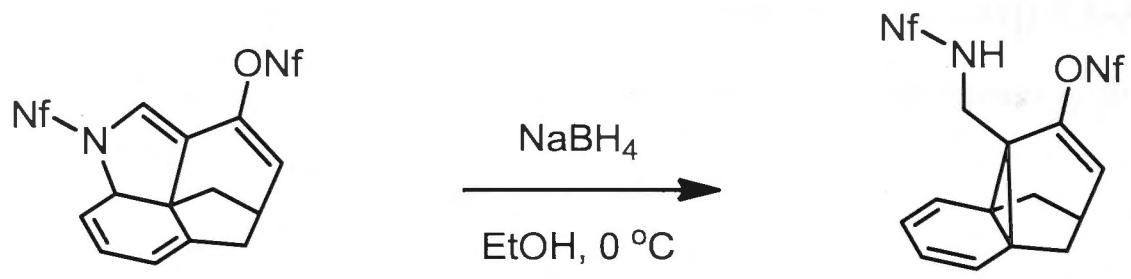
MS (EI, 70eV) *m/z* 763 ($M^{+\bullet}$, 100%), 480 (90), 412 (10).

HREIMS found: $M^{+\bullet}$, 762.9796. $C_{21}H_{11}F_{18}NO_5S_2$ requires $M^{+\bullet}$, 762.9791.

mp 150 °C (with decomposition).

X-ray (The structure was not solved to precision due to presence of two nonaflate groups. It is therefore not included in the Appendices).

(2*s*,4a*r*,4b*R*,8a*S*)-4a-([Nonafluoromethylsulfonamido]methyl)-2,4a-dihydro-1*H*-2,4b-methanocyclopropa[1,2:1,3]dibenzen-4-yl nonafluoromethanesulfonate (3.49)



3.48 **3.49**

A magnetically stirred solution of aza-fenestrane **3.48** (30 mg, 0.039 mmol) in dry ethanol (1 mL) was treated with $NaBH_4$ (2 mg, 0.05 mmol). If the reaction was too sluggish another 2 mg of $NaBH_4$ was added. After 48 h the reaction mixture was diluted with diethyl ether (5 mL) and slowly quenched with NH_4Cl (2 mL of a sat. aq. solution). The separated aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjecting the resulting yellow oil to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) yielded, after concentration of the appropriate fractions (R_f = 0.7 in 13:7 v/v hexane/ethyl acetate), the *title compound* ***3.49*** as a clear, yellow oil (16 mg, 53%).

^{1}H-NMR (400 MHz) δ 6.20 (dd, *J* = 7.4, 2.6 Hz, 2H), 6.12 (d, *J* = 8.2 Hz, 1H), 5.99 (dd, *J* = 7.4, 2.6 Hz, 2H), 5.11 (t, *J* = 5.5 Hz, 1H), 3.37 (d, *J* = 5.5 Hz, 2H), 2.52 (m, 1H), 1.72 (dd, *J* = 12.1, 4.8 Hz, 2H), 1.48 (d, *J* = 12.1 Hz, 2H).

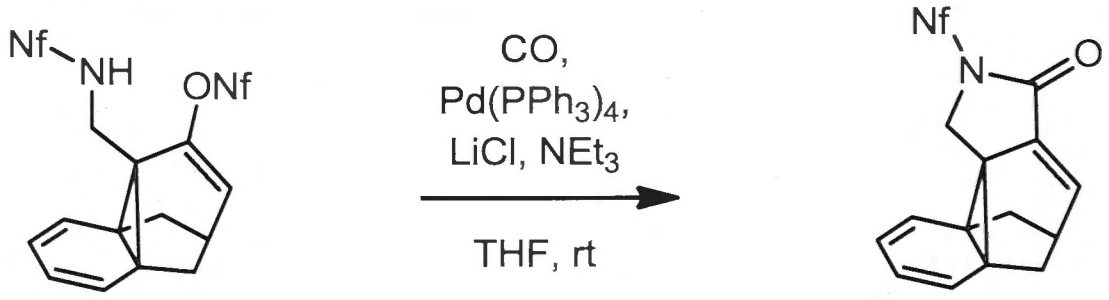
^{13}C-NMR (100 MHz) δ 143.2 (C), 141.6 (C), 126.3 (CH), 121.8 (CH), 116.9 (CH), 39.2 (CH_2), 38.5 (C), 32.8 (CH_2), 26.5 (CH), 20.4 (C) (the signals due to the two C_4F_9-groups were not observed).

IR ν_{max} 3304, 2929, 2858, 1715, 1653, 1426, 1239, 1202 cm^{-1}.

MS (EI, 70eV) *m/z* 482 ($M^{+\bullet}$, 15%), 199 (40), 155 (100), 129 (55), 115 (30), 69 (55).

HREIMS found: $M^{+\bullet}$, 482.0424. $C_{17}H_{13}F_9NO_3S$ requires $M^{+\bullet}$, 482.0472.

(5*s*,6a*R*,10a*S*,10b*s*)-2-([Nonafluoromethyl]sulfonyl)-5,6-dihydro-1*H*-5,10a-methanobenzo-[1,3]cyclopropa[1,2-*h*]isoindol-3(2*H*)-one (3.50)



3.49 **3.50**

A magnetically stirred solution of compound **3.49** (15 mg, 0.020 mmol) in THF (1 mL) was treated with $Pd(PPh_3)_4$ (7 mg, 20 mol%), LiCl (1 mg, 0.03 mmol) and triethylamine (17 µL, 0.12 mmol). The flask was degassed and refilled with carbon monoxide three times before

being stirred vigorously under an atmosphere of carbon monoxide at room temperature for 4 h. After this time the flask was flushed with nitrogen and the mixture concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash column chromatography (silica, 3:1 v/v PS 30-40/diethyl ether elution) gave, after concentration of the appropriate fractions (R_f = 0.6 in 3:1 v/v hexane/ethyl acetate), the *title lactam* ***3.50*** (3 mg, 30%) as a yellow oil, that slowly decomposed in air or under nitrogen atmosphere.

^{1}H-NMR (400 MHz) δ 7.22 (d, *J* = 7.1 Hz, 1H), 6.21 (dd, *J* = 7.4, 2.6 Hz, 2H), 5.92 (dd, *J* = 7.4, 2.6 Hz, 2H), 3.50 (s, 2H), 2.85 (m, 1H), 1.80 (dd, *J* = 12.1, 4.8 Hz, 2H), 1.28 (d, *J* = 12.1 Hz, 2H).

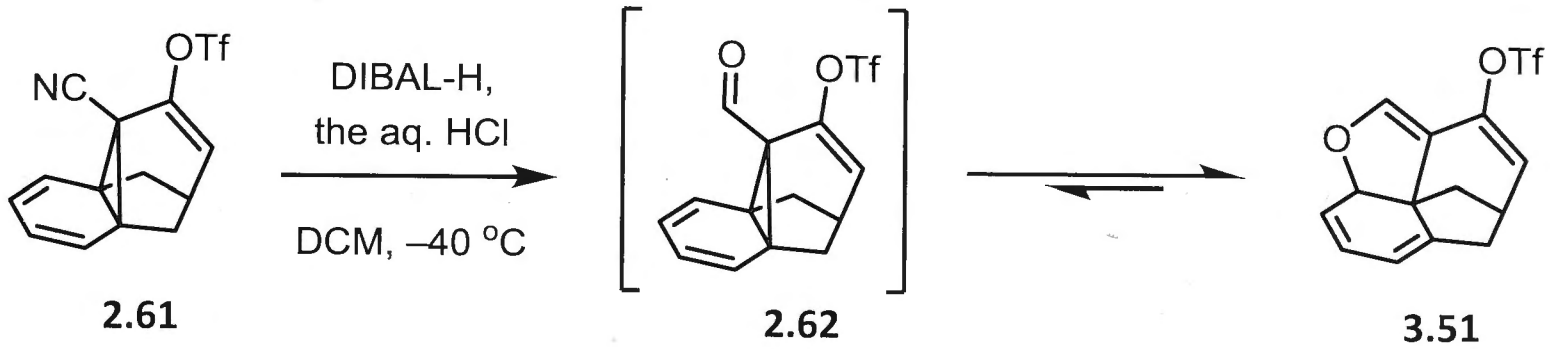
^{13}C-NMR (100 MHz) δ 163.1 (CO), 135.4 (CH), 124.6 (CH), 121.8 (CH), 110.0 (C), 47.4 (CH_2), 38.2 (C), 30.8 (CH), 30.0 (CH_2), 19.0 (C) (the signals due to the C_4F_9-group were not observed).

IR ν_{max} 3041, 2930, 2859 1761, 1651 cm^{-1}.

MS (EI, 70eV) *m/z* 493 ($M^{+\bullet}$, 30%), 210 (100), 167 (40), 115 (15).

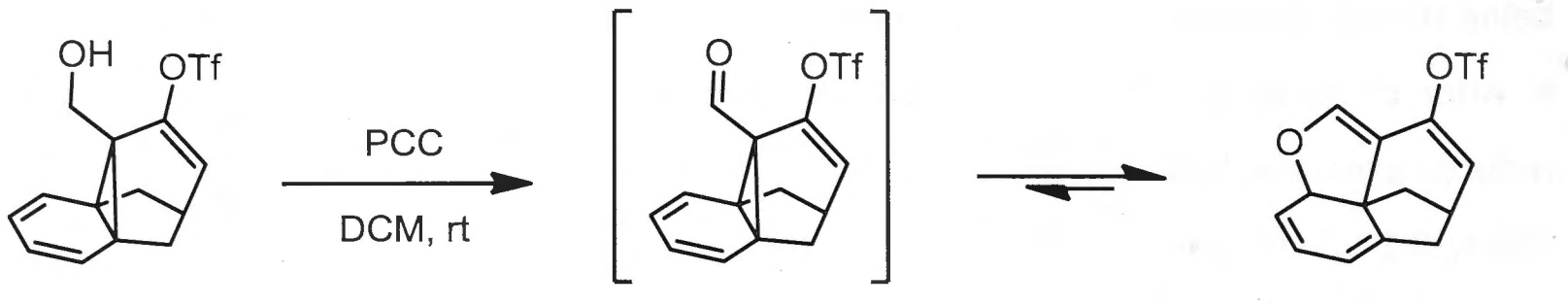
HREIMS found: $[M-SO_2C_4F_9]^{+\bullet}$, 210.0919. $C_{14}H_{12}NO$ requires $[M-SO_2C_4F_9]^{+\bullet}$, 210.0914.

(2a*RS*,2a1*RS*,7*SR*)-2a,6-Dihydro-7*H*-2a1,7-methanocyclohepta[*cd*]benzofuran-9-yl trifluoromethanesulfonate, (Oxa-[5.6.5.6]fenestratetraene, 3.51)



2.61 **2.62** **3.51**

DIBAL-H Reduction of Nitrile ***2.61*** - Under protection from light, a solution of enol triflate **2.61** (500 mg, 1.52 mmol) in DCM (30 mL) maintained at −40°C was treated with DIBAL-H (2.3 mL, 2.3 mmol, 1 M solution in hexane) and stirred for 1 h. The reaction mixture was quenched by adding ethyl acetate (1 mL), allowed to warm to room temperature and treated with 1 M HCl (4 mL) resulting in the appearance of a bright-yellow colour in the organic layer. After 5 min. the mixture became a thick sludge which was stirred vigorously until it formed two clear layers (*ca.* 0.5 h). The separated organic layer was concentrated under reduced pressure and the resulting brown oil subjected to flash column chromatography (silica, 8:2 v/v PS 30-40/diethyl ether elution). Concentration of the appropriate fractions (R_f = 0.9 in 13:7 v/v hexane/ethyl acetate) gave the *title oxa-fenestrane* ***3.51*** (245 mg, 49%) as a bright-yellow oil.



2.63 **2.62** **3.51**

*PCC Re-oxidation of Alcohol **2.63*** – A magnetically stirred solution of alcohol **2.63** (8 mg, 0.024 mmol) in DCM (1 mL) maintained at room temperature was treated with PCC (10 mg, 0.045 mmol). After 2 h the reaction mixture was concentrated under reduced pressure and the resulting brown oil subjected to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) to give two fractions, A and B.

Concentration of fraction **A** (R_f = 0.9 in 13:7 v/v hexane/ethyl acetate), gave the *title oxa-fenestrane **3.51*** (5 mg, 99% brsm) as a clear, colourless oil.

^{1}H-NMR (400 MHz) δ 6.51 (s, 1H), 6.03 (dd, *J* = 9.5, 5.9 Hz, 1H), 5.78 (d, *J* = 7.4 Hz, 1H), 5.70 (m, 1H), 5.67 (d, *J* = 3.9 Hz, 1H), 5.58 (dd, *J* = 9.6, 3.9 Hz, 1H), 2.81 (m, 1H), 2.67 (d, *J* = 16.7 Hz, 1H), 2.59 (dd, *J* = 16.7, 5.8 Hz, 1H), 2.11 (dd, *J* = 10.3, 1.5 Hz, 2H), 1.85 (dd, *J* = 10.3, 4.1 Hz, 2H).

^{13}C-NMR (75 MHz) δ 143.4 (C), 141.7 (C), 139.0 (CH), 125.3 (CH), 119.8 (CH), 119.4 (CH), 118.5 (q, *J* = 320 Hz, CF_3), 116.1 (CH), 116.1 (C, covered), 84.0 (CH), 55.4 (C), 41.3 (CH_2), 38.6 (CH_2), 33.0 (CH).

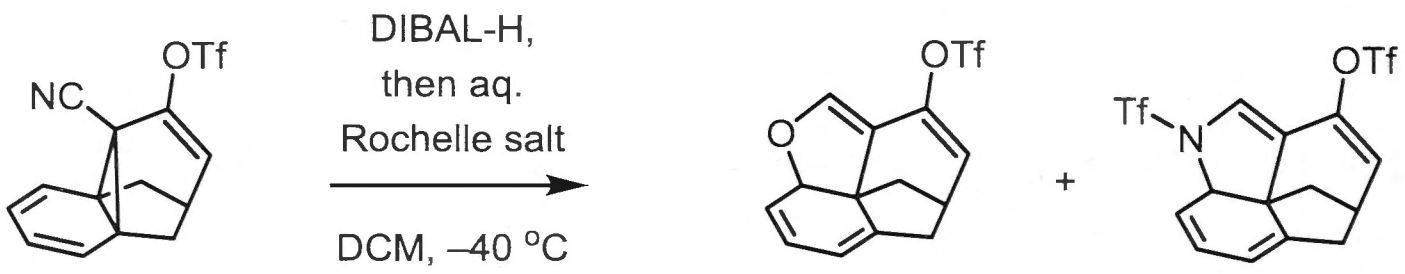
IR ν_{max} 2929, 1663, 1604, 1420, 1213 cm^{-1}.

MS (EI, 70eV) *m/z* 332 ($M^{+\bullet}$, 15%), 167 (10), 97 (45), 69 (100).

HREIMS found: $M^{+\bullet}$, 332.0332. $C_{14}H_{11}F_3O_4S$ requires $M^{+\bullet}$, 332.0330.

Concentration of fraction **B** (R_f = 0.9 in 13:7 v/v hexane/ethyl acetate) gave compound **2.63** (3 mg, 37% recovery) as a colourless solid. This material was identical, in all respects, with an authentic sample.

(2a*RS*,2a1*RS*,7*SR*)-2-([Trifluoromethyl]sulfonyl)-2,2a,6,7-tetrahydro-2a1,7-methanocyclo-hepta[*cd*]indol-9-yl trifluoromethanesulfonate, (Aza-[5.6.5.6]fenestratetraene, 3.52)



2.61 **3.51** **3.52**

Under protection from light, a solution of enol triflate **2.61** (300 mg, 0.911 mmol) in DCM (5 mL) maintained at −78 °C was slowly treated with DIBAL-H (1.8 mL, 1.8 mmol, 1M solution in

hexane) and the reaction mixture stirred for 1 h. The reaction was quenched by adding ethyl acetate (0.5 mL), allowed to warm to room temperature and subsequently treated with Rochelle salt (5 mL of a sat. aq. solution). After stirring vigorously for 1 h it was extracted with DCM (3 x 2 mL), washed with water, dried ($MgSO_4$) and filtered. Subjection of the resulting brown oil to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.9 in 13:7 v/v hexane/ethyl acetate) yielded the title oxa-fenestrane **3.51** (15 mg, 5%) as an unstable pale-yellow oil. This material was, in all respects, identical to an authentic sample.

Concentration of fraction **B** (R_f = 0.8 in 13:7 v/v hexane/ethyl acetate) yielded the *title aza-fenestrane* ***3.52*** (58 mg, 14%) as pale-yellow crystals, which turned brown within minutes.

Compound 3.52

^{1}H-NMR (400 MHz) δ 6.32 (s, 1H), 6.05 (d, *J* = 7.4 Hz, 1H), 6.01 (dd, *J* = 9.3, 5.9 Hz, 1H), 5.79 (m, 1H), 5.58 (dd, *J* = 9.3, 3.3 Hz, 1H), 5.43 (s, 1H), 2.88 (m, 1H), 2.65 (m, 2H), 2.18 (d, *J* = 10.7 Hz, 1H), 1.94 (dd, *J* = 10.7, 4.0 Hz, 2H).

^{13}C-NMR (100 MHz) δ 140.4 (C), 138.8 (C), 127.2 (C), 124.7 (CH), 120.6 (CH), 119.9 (CF_3, *J* = 321 Hz), 119.3 (CH), 118.4 (CF_3, *J* = 320 Hz), 117.8 (CH), 66.0 (CH), 56.1 (C), 42.9 (CH_2), 37.6 (CH_2), 32.9 (CH).

IR ν_{max} 3115, 2941, 1664, 1609, 1423, 1402 cm^{-1}.

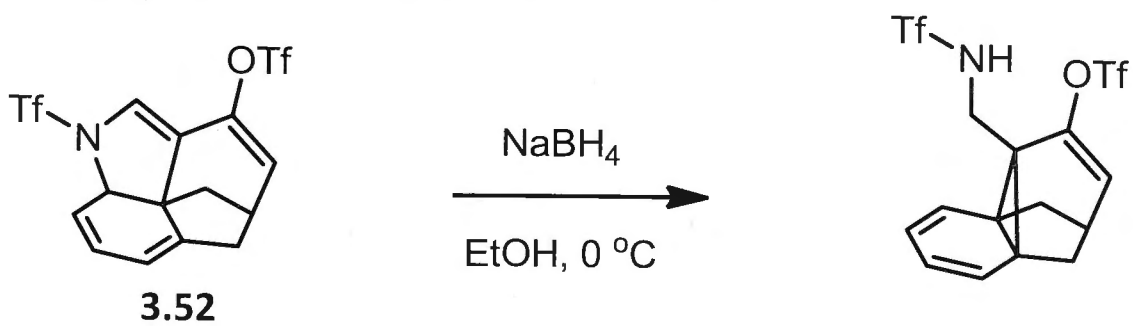
MS (EI, 70eV) *m/z* 463 ($M^{+\bullet}$, 50%), 330 (20), 197 (100), 115 (25), 69 (25).

HREIMS found: $M^{+\bullet}$, 462.9981. $C_{15}H_{11}F_6NO_5S_2$ requires $M^{+\bullet}$, 462.9983.

mp 104-107 °C (strong discolouration prior to melting).

X-ray (see Appendix 5).

(2*s*,4a*r*,4b*R*,8a*S*)-4a-([Trifluoromethylsulfonamido]methyl)-2,4a-dihydro-1*H*-2,4b-methano-cyclopropa[1,2:1,3]dibenzen-4-yl trifluoromethanesulfonate



3.52

A magnetically stirred solution of aza-fenestrane **3.52** (13 mg, 0.028 mmol) in dry ethanol (0.5 mL) was treated with $NaBH_4$ (1 mg, 0.03 mmol). After 1 h further $NaBH_4$ (1 mg, 0.03 mmol) was added. After 48 h the reaction mixture was diluted with diethyl ether (5 mL) and slowly quenched with NH_4Cl (2 mL of a sat. aq. solution). The separated aqueous layer was extracted

with diethyl ether (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting yellow oil to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) yielded, after concentration of the appropriate fractions (R_f = 0.7 in 13:7 v/v hexane/ethyl acetate), the *title compound* (7 mg, 53%) as an off-white solid.

^{1}H-NMR (400 MHz) δ 6.19 (dd, *J* = 7.4, 2.6 Hz, 2H), 6.11 (d, *J* = 8.2 Hz, 1H), 5.99 (dd, *J* = 7.4, 2.6 Hz, 2H), 4.91 (s, 1H), 3.30 (d, *J* = 3.8 Hz, 2H), 2.52 (m, 1H), 1.72 (dd, *J* = 12.1, 4.8 Hz, 2H), 1.47 (d, *J* = 12.1 Hz, 2H).

^{13}C-NMR (100 MHz) δ 141.3 (C), 126.1 (CH), 121.8 (CH), 119.6 (q, *J* = 322 Hz, CF_3), 118.3 (q, *J* = 320 Hz, CF_3), 116.8 (CH), 38.7 (CH_2), 38.5 (C), 32.8 (CH_2), 26.4 (CH), 19.9 (C).

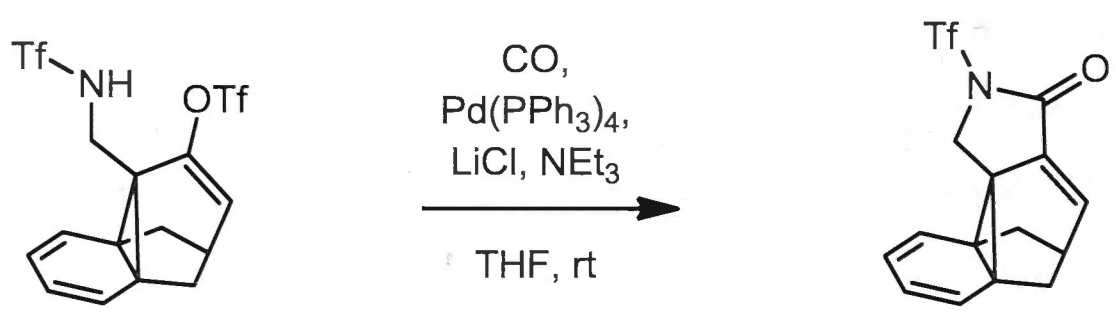
IR ν_{max} 3297, 3047, 2933, 2861, 1656 cm^{-1}.

MS (EI, 70eV) *m/z* 465 ($M^{+\bullet}$, 55%), 332 (15), 199 (30), 155 (100), 115 (40).

HREIMS found: $M^{+\bullet}$, 465.0130. $C_{15}H_{13}F_6NO_5S_2$ requires $M^{+\bullet}$, 465.0139.

mp 75-84 °C.

(5*s*,6a*R*,10a*S*,10b*s*)-2-([Trifluoromethyl]sulfonyl)-5,6-dihydro-1*H*-5,10a-methanobenzo-[1,3]cyclopropa[1,2-*h*]isoindol-3(2*H*)-one



A solution of triflate-protected amine (19 mg, 0.041 mmol) in THF (2 mL) was treated with $Pd(PPh_3)_4$ (6 mg, 10 mol%), LiCl (2 mg, 0.041 mmol) and triethylamine (23 µL, 0.16 mmol) and then the flask evacuated and refilled with carbon monoxide three times. The ensuing reaction mixture was stirred vigorously at room temperature for 1.5 h and then flushed with nitrogen gas to remove excess carbon monoxide. Concentration under reduced pressure and subjection of the resulting yellow oil to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) gave, after concentration of the appropriate fractions (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate), the *title compound* (8 mg, 58%) as a clear, pale-yellow oil.

^{1}H-NMR (400 MHz) δ 7.21 (d, *J* = 7.1 Hz, 1H), 6.20 (dd, *J* = 7.4, 2.7 Hz, 2H), 5.92 (dd, *J* = 7.3, 2.7 Hz, 2H), 3.46 (s, 2H), 2.85 (m, 1H), 1.79 (dd, *J* = 12.1, 4.8 Hz, 2H), 1.28 (d, *J* = 12.1 Hz, 2H).

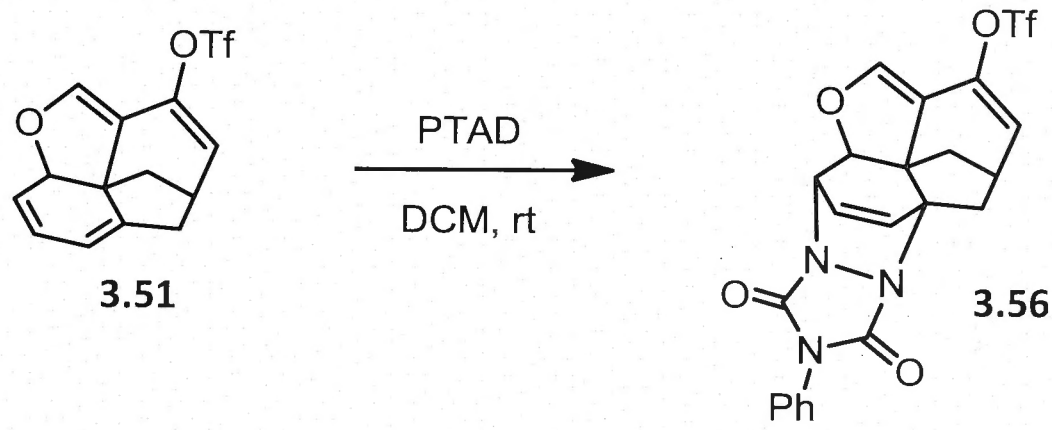
^{13}C-NMR (100 MHz) δ 163.3 (CO), 135.2 (CH), 127.0 (C), 124.6 (CH), 121.8 (CH), 119.5 (q, *J* = 323 Hz, CF_3), 47.1 (CH_2), 38.2 (C), 30.7 (CH), 30.0 (CH_2), 19.0 (C).

IR ν_{max} 3037, 2928, 2858, 1766, 1651 cm^{-1}.

MS (EI, 70eV) *m/z* 343 ($M^{+\bullet}$, 45%), 210 (100), 167 (50), 115 (25).

HREIMS found: $M^{+\bullet}$, 343.0494. $C_{15}H_{12}F_3NO_3S$ requires $M^{+\bullet}$, 343.0490.

(2*RS*,4a1*SR*,6a*SR*,7*SR*,10b*RS*)-8,10-Dioxo-9-phenyl-1,2,6a,7,9,10-hexahydro-8*H*-6-oxa-7a,9,10a-triaza-7,10b-etheno-2,4a1-methanocyclohepta[*cd*]-s-indacen-4-yl trifluoromethanesulfonate (3.56)



3.51 **3.56**

A magnetically stirred solution of oxa-fenestrane **3.51** (30 mg, 0.090 mmol) in DCM (5 mL) maintained at room temperature was treated with PTAD (24 mg, 0.14 mmol), resulting in a bright pink solution which slowly turned orange. After 1.5 h the reaction mixture was concentrated under reduced pressure and the resulting brown solid subjected to flash column chromatography (silica, 3:2 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate), the *title PTAD adduct* ***3.56*** (24 mg, 53%) as powdery, colourless crystals.

^{1}H-NMR (400 MHz) δ 7.47 - 7.34 (complex m, 5H), 6.78 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.40 (dd, *J* = 8.3, 5.4 Hz, 1H), 6.27 (s, 1H), 6.01 (d, *J* = 7.6 Hz, 1H), 5.23 (m, 1H), 5.06 (d, *J* = 4.1 Hz, 1H), 3.97 (q, *J* = 7.6 Hz, 1H), 2.97 (m, 1H), 2.45 (dd, *J* = 11.0, 4.5 Hz, 2H), 2.35 (covered, 1H), 2.30 (d, *J* = 11.0 Hz, 1H).

^{13}C-NMR (100 MHz) δ 156.7 (CO), 155.1 (CO), 141.5 (CH), 140.6 (C), 136.4 (CH), 130.8 (C), 129.2 (CH), 128.6 (CH), 125.9 (CH), 125.8 (CH), 123.6 (CH), 118.4 (q, *J* = 320 Hz, CF_3), 114.3 (C), 80.1 (CH), 72.8 (C), 63.6 (C), 52.4 (CH), 38.4 (CH_2), 35.7 (CH_2), 35.6 (CH).

IR ν_{max} 3076, 2920, 2850, 1774, 1715, 1666, 1407 cm^{-1}.

MS (EI, 70eV) *m/z* 507 ($M^{+\bullet}$, 20%), 374 (10), 240 (100), 121 (25).

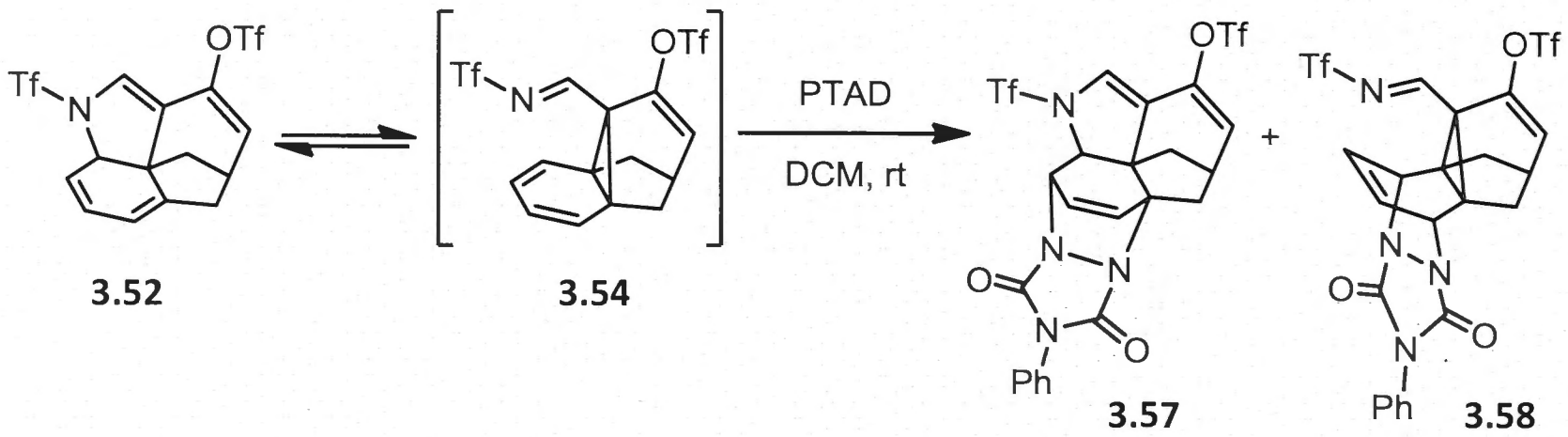
HREIMS found: $M^{+\bullet}$, 507.0714. $C_{22}H_{16}F_3N_3O_6S$ requires $M^{+\bullet}$, 507.0712.

mp 114-119 °C (strong discolouration prior to melting).

X-ray (see Appendix 6).

(2*RS*,4a1*RS*,6a*SR*,7*SR*,10b*RS*)-8,10-Dioxo-9-phenyl-6-([trifluoromethyl]sulfonyl)-2,6,6a,7,9,10-hexahydro-1*H*,8*H*-6,7a,9,10a-tetraaza-7,10b-etheno-2,4a1-methanocyclohepta[*cd*]-s-indacen-4-yl trifluoromethanesulfonate (3.57) and

(2*R*,4a*S*,4b*R*,11*R*,11a*S*)-7,9-Dioxo-8-phenyl-4a-([*E*]-([{trifluoromethyl}sulfonyl]imino)methyl)-2,4a,8,9-tetrahydro-1*H*,5*H*,7*H*,11*H*-5,11-etheno-2,4b-methanobenzo[1,3]cyclopropa[1,2-*d*][1,2,4]triazolo[1,2-a]pyridazin-4-yl trifluoromethanesulfonate (3.58)



3.52 **3.54** **3.57** **3.58**

A magnetically stirred solution of aza-fenestrane **3.52** (40 mg, 0.085 mmol) in DCM (4 mL) maintained at room temperature was treated with PTAD (22 mg, 0.13 mmol). After 1.5 h the dark red-brown reaction mixture was concentrated under reduced pressure and the resulting brown oil subjected to flash column chromatography (silica, 3:2 v/v PS 30-40/diethyl ether elution) to give two fractions, A and B.

Concentration of fraction **A** (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate) yielded the *title PTAD adduct* ***3.57*** (27 mg, 63%) as a colourless wax.

Compound 3.57

^{1}H-NMR (400 MHz) δ 7.45 (m, 2H), 7.41-7.34 (complex m, 3H), 6.82 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.51 (dd, *J* = 8.3, 5.4 Hz, 1H), 6.34 (d, *J* = 7.8 Hz, 1H), 6.20 (s, 1H), 5.37 (m, 1H), 4.77 (d, *J* = 3.4 Hz, 1H), 4.13 (dd, *J* = 15.4, 7.7 Hz, 1H), 3.07 (m, 1H), 2.54 (dd, *J* = 11.4, 4.7 Hz, 1H), 2.37-2.31 (partially covered, 3H).

^{13}C-NMR (100 MHz) δ 156.7 (CO), 154.6 (CO), 139.9 (C), 136.2 (CH), 130.6 (C), 129.2 (CH), 128.9 (CH), 128.8 (CH), 126.3 (CH), 125.8 (CH), 123.2 (C), 123.0 (CH), 119.7 (q, *J* = 323 Hz, CF_3), 118.4 (q, *J* = 320 Hz, CF_3), 72.2 (C), 64.4 (C), 62.5 (CH), 52.6 (CH), 37.7 (CH_2), 36.9 (CH_2), 35.3 (CH).

IR ν_{max} 3456, 3114, 2963, 2918, 2850, 1775, 1722, 1614, 1503, 1407 cm^{-1}.

MS (EI, 70eV) *m/z* 505 ($[M-Tf]^{+\bullet}$, 10%), 398 (10), 240 (100), 121 (35), 93 (25).

HREIMS found: $[M-Tf]^{+\bullet}$, 505.0847. $C_{22}H_{16}F_3N_4O_5S$ requires $[M-Tf]^{+\bullet}$, 505.0793.

Concentration of fraction **B** (R_f = 0.4 in 13:7 v/v hexane/ethyl acetate) yielded the *title symmetrical PTAD adduct* ***3.58*** (4 mg, 9%) as a colourless wax.

Compound 3.58

^{1}H-NMR (400 MHz) δ 7.49-7.38 (complex m, 5H), 6.59 (dd, *J* = 4.3, 3.1 Hz, 2H), 6.26 (d, *J* = 8.2 Hz, 1H), 5.47 (t, *J* = 3.4 Hz, 2H), 3.03 (m, 1H), 2.27 (dd, *J* = 12.8, 5.0 Hz, 2H), 1.44 (d, *J* = 12.8 Hz, 2H).

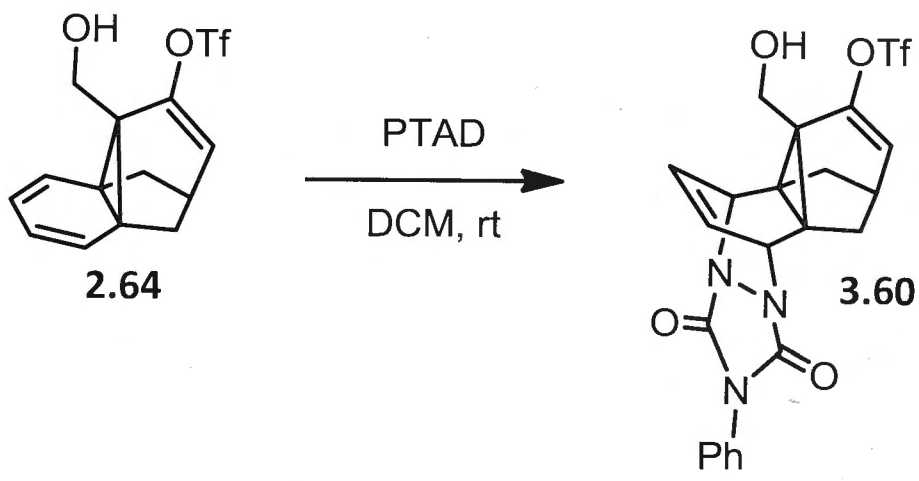
^{13}C-NMR (100 MHz) δ 156.6 (CO), 138.8 (C), 130.7 (C), 129.3 (CH), 128.8 (CH), 128.8 (CH), 125.5 (CH), 121.4 (CH), 113.8 (CH), 54.5 (CH), 35.7 (C), 33.4 (CH), 27.2 (CH_2), 15.3 (C) (the signals due to the CF_3-group were not observed).

IR ν_{max} 3074, 2935, 2235, 1778, 1722 cm^{-1}.

MS (EI, 70eV) *m/z* 638 ($M^{+\bullet}$, 1%), 504 (5), 329 (75), 240 (45), 196 (70), 168 (100), 141 (95), 119 (75).

HREIMS found: $M^{+\bullet}$, 638.0365. $C_{23}H_{16}F_6N_4O_7S_2$ requires $M^{+\bullet}$, 638.0358.

(2*R*,4a*S*,4b*R*,11*R*,11a*S*)-4a-(Hydroxymethyl)-7,9-dioxo-8-phenyl-2,4a,8,9-tetrahydro-1*H*,5*H*,7*H*,11*H*-5,11-etheno-2,4b-methanobenzo[1,3]cyclopropa[1,2-*d*][1,2,4]triazolo[1,2-a]pyridazin-4-yl trifluoromethanesulfonate (3.60)



2.64 **3.60**

A magnetically stirred solution of alcohol **2.63** (7 mg, 0.02 mmol) in DCM (2 mL) maintained at room temperature was treated with PTAD (8 mg, 0.04 mmol), resulting in a bright-pink solution that slowly turned yellow. After 1 h the reaction mixture was concentrated under reduced pressure and the ensuing brown oil subjected to flash column chromatography (silica, 1:1 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 13:7 v/v hexane/ethyl acetate), the *title PTAD adduct* ***3.60*** (8 mg, 76%) as a colourless, crystalline solid.

^{1}H-NMR (300 MHz) δ 7.49-7.33 (complex m, 5H), 6.45 (dd, *J* = 4.2, 3.2 Hz, 2H), 6.18 (d, *J* = 8.2 Hz, 1H), 5.40 (t, *J* = 3.2 Hz, 2H), 4.30 (d, *J* = 5.2 Hz, 2H), 2.85 (m, 1H), 2.21 (dd, *J* = 12.3, 5.0 Hz, 2H), 1.67 (t, *J* = 5.2 Hz, OH), 1.33 (d, *J* = 12.3 Hz, 2H).

^{13}C-NMR (100 MHz) δ 157.0 (CO), 144.1 (C), 129.2 (CH), 128.4 (CH), 126.9 (CH), 125.6 (CH), 122.2 (CH), 56.6 (CH), 54.6 (CH_2), 33.4 (CH), 32.4 (C), 28.6 (CH_2) (signals due to three carbons are obscured or overlapping).

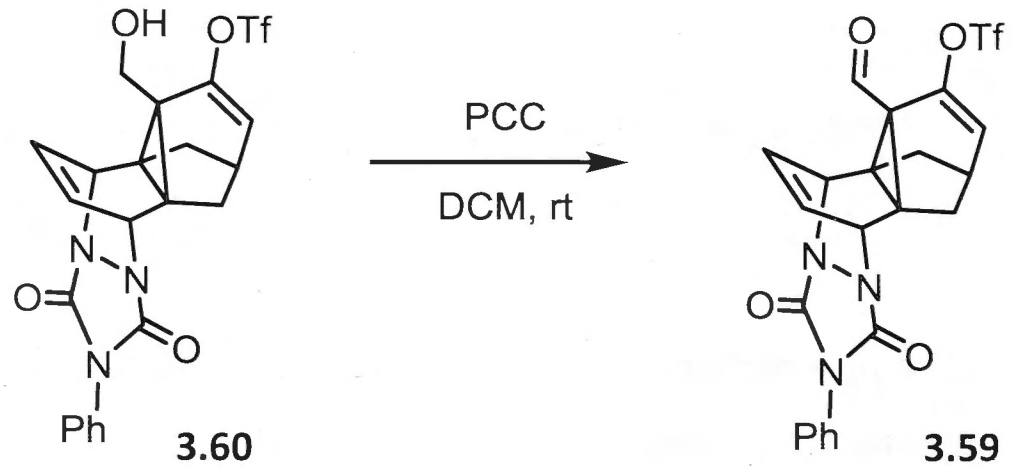
IR ν_{max} 3464, 3073, 2933, 2863, 2252, 1773, 1711, 1660, 1416 cm^{-1}.

MS (EI, 70eV) *m/z* 509 ($M^{+\bullet}$, 50%), 332 (100), 171 (80), 115 (35).

HREIMS found: $M^{+\bullet}$, 509.0866. $C_{22}H_{18}F_3N_3O_6S$ requires $M^{+\bullet}$, 509.0868.

mp 104-108 °C.

(2*R*,4a*R*,4b*R*,11*R*,11a*S*)-4a-Formyl-7,9-dioxo-8-phenyl-2,4a,8,9-tetrahydro-1*H*,5*H*,7*H*,11*H*-5,11-etheno-2,4b-methanobenzo[1,3]cyclopropa[1,2-*d*][1,2,4]triazolo[1,2-*a*]pyridazin-4-yl trifluoromethanesulfonate (3.59)



A magnetically stirred solution of compound **3.60** (8 mg, 0.02 mmol) in DCM (1 mL) maintained at room temperature was treated with PCC (4 mg, 0.02 mmol). After 1 h the orange reaction mixture was concentrated under reduced pressure and the ensuing brown oil filtered through a short silica plug (1:1 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 13:7 v/v hexane/ethyl acetate), the *title aldehyde* ***3.59*** (7 mg, 88%) as colourless needles.

^{1}H-NMR (300 MHz) δ 9.70 (s, 1H), 7.49 - 7.30 (complex m, 5H), 6.38 (m, 2H), 6.20 (d, *J* = 8.2 Hz, 1H), 5.42 (t, *J* = 3.6 Hz, 2H), 3.02 (m, 1H), 2.17 (dd, *J* = 12.5, 4.8 Hz, 2H), 1.45 (d, *J* = 12.5 Hz, 2H).

^{13}C-NMR (100 MHz) δ 194.0 (CO), 156.7 (CO), 141.4 (C), 131.0 (CH), 130.8 (C), 129.2 (CH), 128.6 (CH), 125.5 (CH), 120.7 (CH), 54.8 (CH), 34.3 (CH), 33.2 (C), 29.7 (CH_2), 27.7 (C) (the signals due to the CF_3-group were not observed).

IR ν_{max} 2962, 2917, 2849, 2253, 1771, 1714 cm^{-1}.

MS (EI, 70eV) *m/z* 507 ($M^{+\bullet}$, 40%), 374 (10), 332 (40), 240 (100), 171 (40), 128 (60).

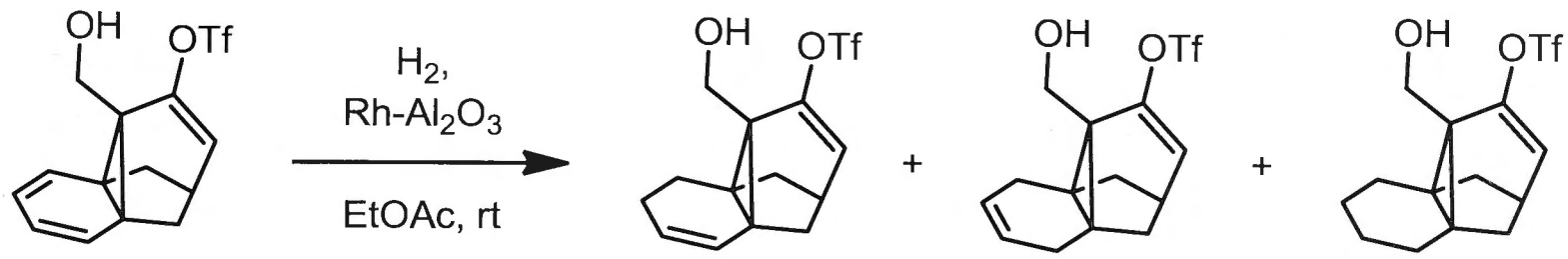
HREIMS found: $M^{+\bullet}$, 507.0700. $C_{22}H_{16}F_3N_3O_6S$ requires $M^{+\bullet}$, 507.0712

mp 84-90 °C.

(2*SR*,4a*RS*,4b*RS*,8a*RS*)-4a-(Hydroxymethyl)-2,4a,5,6-tetrahydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzen-4-yl trifluoromethanesulfonate (3.61),

(2r,4as,4b*RS*,8a*SR*)-4a-(Hydroxymethyl)-2,4a,5,8-tetrahydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzen-4-yl trifluoromethanesulfonate (3.62) and

(2r,4as,4b*RS*,8a*SR*)-4a-(Hydroxymethyl)-2,4a,5,6,7,8-hexahydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzen-4-yl trifluoromethanesulfonate (3.63)



2.63 **3.61** **3.62** **3.63**

A magnetically stirred solution of alcohol **3.63** (40 mg, 0.12 mmol) in ethyl acetate (2 mL) was treated with rhodium on alumina (12 mg, 5 mol%) and the flask degassed and refilled with hydrogen gas three times. The reaction mixture was stirred vigorously at room temperature for 0.17 h and then flushed with nitrogen to remove excess hydrogen gas. The resulting mixture was filtered through a short plug of silica gel and the filtrate concentrated under reduced pressure. Subjection of the resulting colourless oil to flash column chromatography (silica, 3:1 v/v PS 30-40/diethyl ether elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.7 in 13:7 v/v hexane/ethyl acetate) yielded a 1:1 mixture of the *title alcohols **3.62** and **3.63*** (10 mg, 25%) as a colourless solid. Fraction **A** was resubjected to flash column chromatography on silver-impregnated silica gel to separate the two compounds for the purposes of characterisation.

Compound 3.62

^{1}H-NMR (400 MHz) δ 5.92 (d, *J* = 8.2 Hz, 1H), 5.76 (s, 2H), 3.93 (s, 2H), 2.59 (m, 1H), 2.48 (s, 4H), 1.55 (dd, *J* = 11.9, 4.7 Hz, 2H), 1.33 (d, *J* = 11.9 Hz, 2H).

^{13}C-NMR (100 MHz) δ 146.7 (C), 125.5 (CH), 116.1 (CH), 57.8 (CH_2), 36.6 (CH_2), 34.0 (C), 30.2 (CH), 26.4 (C), 23.3 (CH_2) (the signals due to the CF_3-group were not observed).

IR ν_{max} 3325, 3033, 2921, 2851, 1654, 1421, 1400 cm^{-1}.

MS (EI, 70eV) *m/z* 336 ($M^{+\bullet}$, 5%), 318 (100), 185 (45), 129 (40).

HREIMS found: $M^{+\bullet}$, 336.0643. $C_{14}H_{15}F_3O_4S$ requires $M^{+\bullet}$, 336.0643.

mp 53-61 °C.

Compound 3.63

^{1}H-NMR (400 MHz) δ 5.87 (d, *J* = 8.2 Hz, 1H), 4.04 (s, 2H), 2.52 (m, 1H), 1.98 (m, 2H), 1.80 (m, 2H), 1.53 (dd, *J* = 12.0, 4.7 Hz, 2H), 1.41 (m, 4H), 1.26 (d, *J* = 12.0 Hz, 2H).

^{13}C-NMR (100 MHz) δ 146.8 (C), 118.4 (q, *J* = 321 Hz, CF_3), 115.9 (CH), 58.5 (CH_2), 37.3 (CH_2), 34.5 (C), 30.3 (CH), 28.4 (C), 22.1 (CH_2), 21.5 (CH_2).

IR ν_{max} 3335, 2941, 2857, 1655, 1419 cm^{-1}.

MS (EI, 70eV) *m/z* 338 ($M^{+\bullet}$, 1%), 320 (100), 187 (65), 159 (70), 145 (70), 91 (80).

HREIMS found: $[M-OH]^{+\bullet}$, 320.0699. $C_{14}H_{15}F_3O_3S$ requires $[M-OH]^{+\bullet}$, 320.0694.

mp 73-75 °C.

Concentration of fraction **B** (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate) yielded the *title alcohol* ***3.61*** (8 mg, 20%) as fine, colourless needles.

Compound 3.61

^{1}H NMR (400 MHz) δ 5.99 (m, 2H), 5.96 (d, *J* = 8.2 Hz, 1H), 3.94 (d, *J* = 12.7 Hz, 2H), 2.66 (m, 1H), 2.16 (m, 1H), 2.06 (m, 3H), 1.62 (dd, *J* = 11.9, 4.8 Hz, 1H), 1.56 (dd, *J* = 11.9, 4.8 Hz, 1H), 1.31 (d, *J* = 7.0 Hz, 1H), 1.26 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (MHz) δ 146.1 (C), 131.3 (CH), 124.3 (CH), 121.6 (q, *J* = 320 Hz, CF_3), 116.9 (CH), 58.3 (CH_2), 40.2 (C), 35.9 (CH_2), 33.0 (CH_2), 30.2 (CH), 29.3 (C), 29.3 (C), 22.7 (CH_2), 20.3 (CH_2).

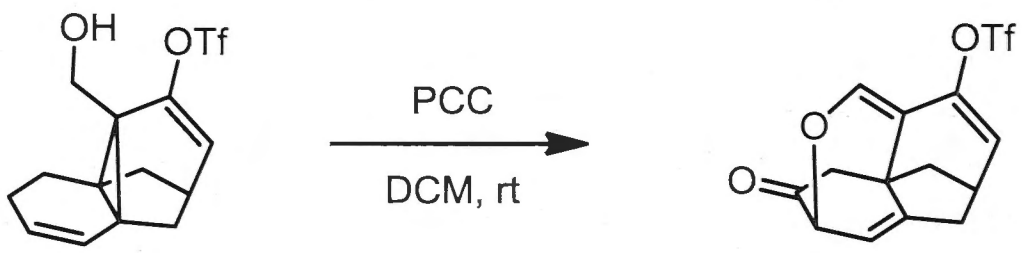
IR ν_{max} 3307, 3031, 2927, 2853, 1652, 1419 cm^{-1}.

MS (EI, 70eV) *m/z* 336 ($M^{+\bullet}$, 1%), 318 (100), 185 (60), 129 (40), 115 (30).

HREIMS found: $M^{+\bullet}$, 336.0641. $C_{14}H_{15}F_3O_4S$ requires $M^{+\bullet}$, 336.0643.

mp 54-56 °C.

2-Oxo-2,3,8,9-tetrahydro-1*H*-8,10a-methano-3,10-(metheno)cyclohepta-[*c*]oxepin-6-yl trifluoromethanesulfonate, (Oxa-[5.6.7.6]fenestratrienone, 3.64)



3.61 **3.64**

PCC-Oxidation of Alcohol ***3.61*** - A magnetically stirred solution of alcohol **3.61** (8 mg, 0.024 mmol) in DCM (1 mL) maintained at room temperature was treated with PCC (14 mg, 0.065 mmol). After 12 h the brown reaction mixture was filtered through a short plug of silica gel and the filtrate concentrated under reduced pressure. Subjection of the resulting clear oil to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) yielded, after concentration of the appropriate fractions (R_f = 0.2 in 13:7 v/v hexane/ethyl acetate) the *title fenestrane* ***3.64*** (5 mg, 61%) as a colourless oil, which rapidly turned pale-yellow.

^{1}H NMR (500 MHz) δ 6.61 (s, 1H), 6.14 (s, 1H), 5.99 (d, *J* = 7.8 Hz, 1H), 4.72 (t, *J* = 2.7 Hz, 1H), 3.05 (m, 1H), 2.87 (m, 2H), 2.37 (dd, *J* = 13.2, 3.4 Hz, 1H), 2.29 (dd, *J* = 13.2, 2.0 Hz, 1H), 1.92 (dd, *J* = 11.2, 2.2 Hz, 1H), 1.77 (dd, *J* = 11.2, 4.4 Hz, 1H).

^{13}C NMR (125 MHz) δ 190.8 (CO), 177.0 (C), 143.6 (C), 137.8 (CH), 122.5 (CH), 119.9 (CH), 118.4 (q, *J* = 320 Hz, CF_3), 115.1 (C), 75.6 (CH), 41.8 (C), 40.4 (CH_2), 38.8 (CH_2), 33.7 (CH), 31.2 (CH_2).

IR ν_{max} 2928, 1673, 1646, 1606, 1419 cm^{-1}.

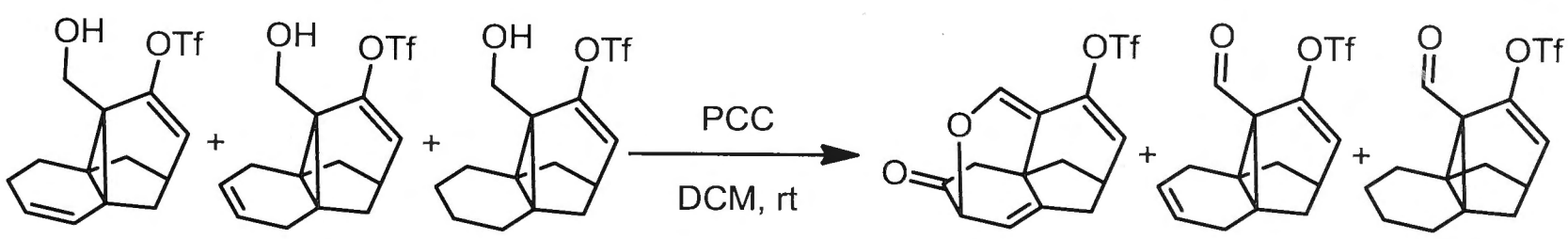
MS (EI, 70eV) *m/z* 348 ($M^{+\bullet}$, 100%), 279 (15), 215 (30), 115 (20).

HREIMS found: $M^{+\bullet}$, 348.0279. $C_{14}H_{11}F_3O_5S$ requires $M^{+\bullet}$, 348.0279.

(3*RS*,8*SR*,10a*RS*)-2-Oxo-2,3,8,9-tetrahydro-1*H*-8,10a-methano-3,10-(metheno)cyclohepta-[*c*]oxepin-6-yl trifluoromethanesulfonate (3.64),

(2r,4ar,4b*RS*,8a*SR*)-4a-Formyl-2,4a,5,8-tetrahydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]di-benzen-4-yl trifluoromethanesulfonate (3.62-ox) and

(2r,4ar,4b*RS*,8a*SR*)-4a-Formyl-2,4a,5,6,7,8-hexahydro-1*H*-2,4b-methanocyclopropa-[1,2:1,3]dibenzen-4-yl trifluoromethanesulfonate (3.63-ox)



3.61 **3.62** **3.63** **3.64** **3.62-ox** **3.63-ox**

*PCC-Oxidation of a Mixture of Alcohols **3.61**, **3.62** and **3.63*** - A magnetically stirred solution of alcohols **3.61 - 3.63** (80 mg of a 1:1:1 mixture, 0.080 mmol of each alcohol) in DCM (3 mL) maintained at room temperature was treated with PCC (100 mg, 0.480 mmol). After 22 h the brown reaction mixture was filtered through a short plug of silica gel and concentrated under reduced pressure. Subjection of the resulting clear oil to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate) yielded the *title aldehyde **3.62-ox*** (15 mg, 56% based on content of alcohol **3.62** in the mixture) as a colourless solid. The *title aldehyde **3.63-ox*** proved to be unstable and was only found as a trace mixed with fraction **A**.

Compound 3.62-ox

^{1}H-NMR (400 MHz) δ 9.38 (s, 1H), 5.94 (d, *J* = 8.2 Hz, 1H), 5.79 (s, 2H), 2.74 – 2.55 (partially covered, 5H), 1.67 (dd, *J* = 12.2, 4.8 Hz, 2H), 1.43 (d, *J* = 12.2 Hz, 2H).

^{13}C-NMR (100 MHz) δ 193.7 (CO), 142.4 (C), 125.0 (CH), 118.2 (CH), 36.3 (CH_2), 33.7 (C), 29.4 (CH), 24.5 (C), 23.7 (CH_2).

IR ν_{max} 3033, 2928, 2852, 1704, 1653, 1420 cm^{-1}.

MS (EI, 70eV) *m/z* 334 ($M^{+\bullet}$, 100%), 267 (35), 173 (50), 155 (55), 131 (65), 115 (50), 91 (70).

HREIMS found: $M^{+\bullet}$, 334.0488. $C_{14}H_{13}F_3O_4S$ requires $M^{+\bullet}$, 334.0487.

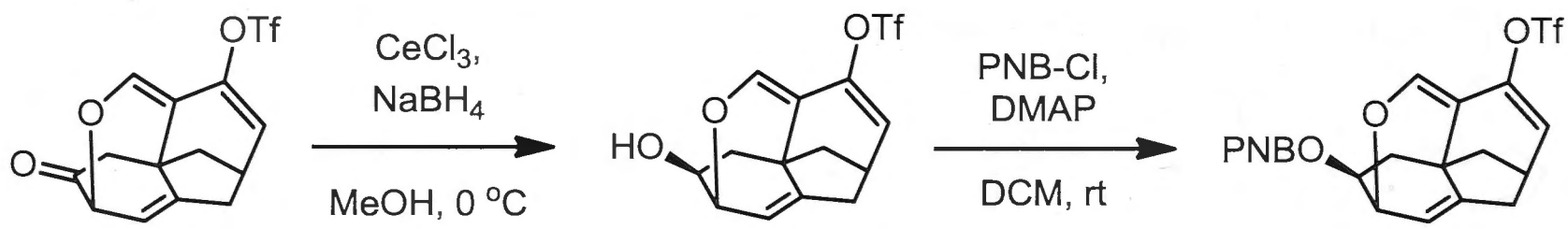
mp 86-89 °C.

Compound 3.63-ox

^{1}H-NMR (400 MHz) δ 9.89 (s, 1H), 5.96 (d, *J* = 8.2 Hz, 1H), 1.97 (t, *J* = 6.5 Hz, 4H), 1.69 (dd, *J* = 12.2, 4.8 Hz, 2H), 1.58 (m, 4H), 1.37 (d, *J* = 12.2 Hz, 2H).

Concentration of fraction **B** (R_f = 0.5 in 13:7 v/v hexane/ethyl acetate) yielded the *title fenestrane* ***3.64*** (7 mg, 25% based on content of alcohol **3.61** in the mixture) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample.

(2*SR*,3*RS*,8*SR*,10a*RS*)-6-([{Trifluoromethyl}sulfonyl]oxy)-2,3,8,9-tetrahydro-1*H*-8,10a-methano-3,10-(metheno)cyclohepta[*c*]oxepin-2-yl 4-nitrobenzoate (3.65)



3.64 **3.65**

Step i - A magnetically stirred solution of ketone **3.64** (10 mg, 0.035 mmol) and $CeCl_3 \cdot 7H_2O$ (32 mg, 0.086 mmol) in MeOH (2 mL) maintained at 0 °C was treated with $NaBH_4$ (2 mg, 0.05 mmol). After 0.17 h the reaction was quenched with water (3 mL), the mixture extracted with DCM (3 x 1 mL) and the separated organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection to flash column chromatography (silica, 1:1 v/v PS 30-40/diethyl ether elution) gave, after concentration of the appropriate fractions (R_f = 0.3 in 13:7 v/v hexane/ethyl acetate), the *title intermediate alcohol* (10 mg, 82%) as a clear, colourless oil.

Title intermediate alcohol

^{1}H-NMR (400 MHz) δ 6.56 (s, 1H), 5.91 (d, *J* = 7.8 Hz, 1H), 5.51 (s, 1H), 4.70 (m, 1H), 4.47 (s, 1H), 2.88 (m, 1H), 2.62 (m, 1H), 2.56 (m, 1H), 2.32 (dd, *J* = 13.0, 4.4 Hz, 1H), 2.00 (dd, *J* = 13.0, 1.5 Hz, 1H), 1.80 (d, *J* = 10.9 Hz, 1H), 1.62 (dd, *J* = 10.9, 4.2 Hz, 1H).

^{13}C-NMR (100 MHz) δ 150.9 (C), 137.0 (CH), 120.9 (CH), 119.3 (CH), 117.9 (C), 110.0 (C), 73.1 (CH), 71.9 (CH), 39.0 (CH_2), 38.8 (CH_2), 33.7 (CH), 30.8 (CH_2), 30.3 (C).

IR ν_{max} 3401, 2965, 1648 cm^{-1}.

MS (EI, 70eV) *m/z* 350 ($M^{+\bullet}$, 55%), 171 (100), 129 (35), 115 (35), 91 (45).

HREIMS found: $M^{+\bullet}$, 350.0443. $C_{14}H_{13}F_3O_5S$ requires $M^{+\bullet}$, 350.0436.

Step ii - A magnetically stirred solution of the thus obtained alcohol (12 mg, 0.029 mmol) in DCM (1 mL) maintained at room temperature was treated with DMAP (4 mg, 0.03 mmol) and 4-nitrobenzoyl chloride (6 mg, 0.03 mmol). After 1 h the solvent was evaporated and the resulting colourless oil subjected to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether – diethyl ether gradient elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 13:7 v/v hexane/ethyl acetate), the *title PNB-ester* ***3.65*** (13 mg, 93%) as a colourless wax.

^{1}H-NMR (400 MHz) δ 8.30 (d, *J* = 8.5 Hz, 2H), 8.23 (d, *J* = 9.0 Hz, 2H), 6.57 (s, 1H), 5.93 (d, *J* = 7.7 Hz, 1H), 5.82 (m, 1H), 5.55 (s, 1H), 5.03 (m, 1H), 2.93 (m, 1H), 2.68 (m, 2H), 2.37 (dd, *J* = 13.0, 4.1 Hz, 1H), 2.13 (dd, *J* = 13.0, 1.7 Hz, 1H), 1.86 (d, *J* = 10.9 Hz, 1H), 1.70 (dd, *J* = 10.9, 4.1 Hz, 1H).

^{13}C-NMR (125 MHz) δ 146.5 (CO), 155.0 (C), 150.7 (C), 144.3 (C), 137.4 (CH), 135.4 (C), 130.9 (CH), 123.6 (CH), 120.5 (CH), 117.0 (C), 114.8 (CH), 75.5 (CH), 69.6 (CH), 39.4 (CH_2), 39.0 (CH_2), 33.7 (CH), 31.0 (CH_2), 29.7 (C).

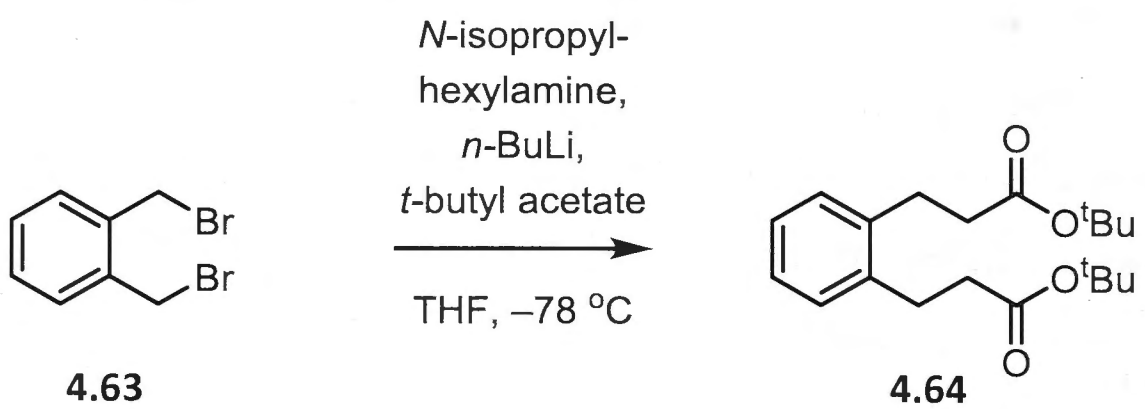
IR ν_{max} 3450, 3113, 2960, 2849, 1725, 1650, 1608 cm^{-1}.

MS (EI, 70eV) *m/z* 499 ($M^{+\bullet}$, 100%), 366 (15), 332 (30), 304 (85), 115 (35), 91 (45).

HREIMS found: $M^{+\bullet}$, 499.0551. $C_{21}H_{16}F_3NO_8S$ requires $M^{+\bullet}$, 499.0549.

6.4. Experimental Procedures for Chapter 4

Di-tert-butyl 3,3'-(1,2-phenylene)dipropanoate (4.64)

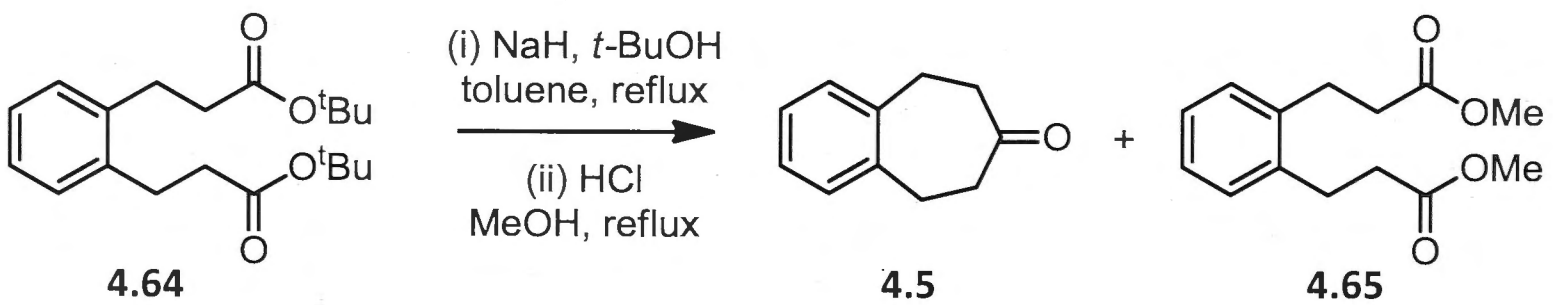


4.63 **4.64**

Following a literature procedure,[10] a magnetically stirred solution of *N*-isopropylhexylamine (8.2 mL, 50 mmol) in THF (40 mL) maintained under a nitrogen atmosphere at −78 °C was slowly treated with a solution of *n*-BuLi (18.4 mL, 46.0 mmol, 2.5 M in hexane). After 0.33 h *t*-butyl acetate (6.7 mL, 50 mmol) was added dropwise, keeping the temperature below −68 °C. The reaction mixture was stirred for another 0.33 h after which time a solution of *o*-dibromoxylene (**4.63**) (5.28 g, 20.0 mmol) in THF (30 mL) was added slowly. The reaction mixture was then stirred at −30 °C for 2.5 h then allowed to warm to room temperature overnight. The reaction was quenched with HCl (50 mL of a 1 M aq. solution) and poured into brine (50 mL) before being extracted with diethyl ether (3 x 20 mL), washed with HCl (20 mL of a 1 M aq. solution), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **4.64**[10] as a pale-yellow oil that was used without further purification in the next step of the reaction sequence.

^{1}H NMR (300 MHz) δ 7.14 (s, 4H), 2.92 (m, 4H), 2.51 (m, 4H), 1.42 (s, 18H).

8,9-Dihydro-5*H*-benzo[7]annulen-7(6*H*)-one (4.5) and Dimethyl 3,3'-(1,2-phenylene)dipropanoate (4.65)



4.64 **4.5** **4.65**

Method 1: Step i - A magnetically stirred suspension of NaH (1.92 g, 48.0 mmol, 60% in mineral oil, washed with 2 x 10 mL toluene) in toluene (70 mL) was treated with *t*-BuOH (0.20 mL, 2.1 mmol). The ensuing mixture was heated at reflux with rapid stirring and a solution of the crude *t*-butyl ester **4.4**, obtained as described above, in toluene (80 mL) was added dropwise over 3 h. After cooling to room temperature, glacial acetic acid (4.3 mL, 75 mmol) was added, followed by ice water (50 mL). The separated aqueous phase was extracted with ethyl acetate

(2 x 20 mL) and the combined organic layers washed with brine (1 x 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an orange oil that was used without further purification for the next reaction as described immediately below.

Step ii. - A magnetically stirred solution of the above-mentioned orange oil in methanol (20 mL) was treated with HCl (10 mL of a 6 M aq. solution) and the resulting mixture heated at reflux for 3 h before being cooled then poured onto ice and extracted with diethyl ether (2 x 10 mL). The combined organic phases were washed with $NaHCO_3$ (10 mL of a sat. aq. solution,), dried ($MgSO_4$) before being filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash column chromatography (silica, 9:1 v/v PS 30-40/diethyl ether elution) to give two fractions, A and B.

Concentration of fraction **A** (R_f = 0.5 in 17:3 v/v hexane/ethyl acetate) yielded the title 3-benzosuberone **4.5** (1.48 g, 46% over two steps) as a pale-yellow crystalline solid.

Compound 4.5

^{1}H NMR (300 MHz) δ 7.23 (s, 4H), 2.91 (m, 4H), 2.62 (m, 4H).

^{13}C NMR (100 MHz) δ 211.3 (CO), 140.6 (C), 129.1 (CH), 127.1 (CH), 44.6 (CH_2), 30.5 (CH_2).

IR ν_{max} 3019, 2953, 2854, 1699 cm^{-1}.

MS (EI, 70eV) *m/z* 160 ($M^{+\bullet}$, 80%), 117 (100), 84 (60).

HREIMS found: $M^{+\bullet}$, 160.0892. $C_9H_{12}O$ requires $M^{+\bullet}$, 160.0888.

mp 39-41 °C.

These data match those reported by Ewing *et al.*[10]

Concentrations of fraction **B** (R_f = 0.3, 17:3 v/v hexane/ethyl acetate) yielded the *title methyl ester* ***4.65*** (0.940 g, 19%), which resulted from incomplete Dieckmann cyclisation followed by trans-esterification with methanol, as a clear pale-yellow oil.

Compound 4.65

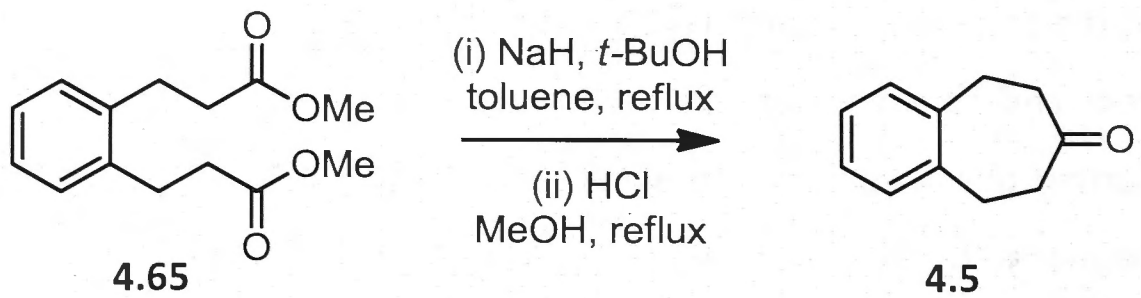
^{1}H NMR (400 MHz) δ 7.16 (s, 4H), 3.68 (s, 6H), 2.98 (m, 4H), 2.61 (m, 4H).

^{13}C NMR (125 MHz) δ 173.2 (CO), 138.2 (C), 128.9 (CH), 126.7 (CH), 51.7 (CH_3), 51.7 (CH_3), 35.1 (CH_2), 27.5 (CH_2).

IR ν_{max} 3062, 2952, 2846, 1734 cm^{-1}.

MS (EI, 70eV) *m/z* 250 ($M^{+\bullet}$, 25%), 219 (20), 186 (60), 158 (75), 117 (100), 91 (35).

HREIMS found: $M^{+\bullet}$, 250.1201. $C_{14}H_{18}O_4$ requires $M^{+\bullet}$, 250.1205.



4.65 **4.5**

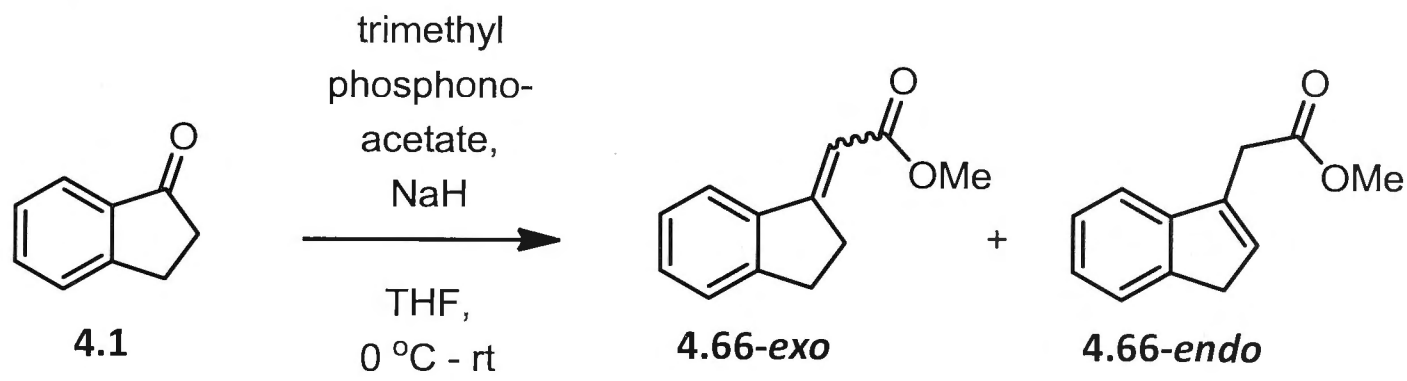
Method 2: A magnetically stirred solution of methyl ester **4.65** (0.940 g, 3.76 mmol) was resubjected to the same Dieckmann cyclisation conditions as described for *Method 1* using NaH (0.39 g, 9.6 mmol, 60% in mineral oil) and *t*-BuOH (0.10 mL, 1.0 mmol) in toluene (20 mL), followed by decarboxylation (HCl, 2 mL of a 6 M aq. solution, and 4 mL methanol). The resulting yellow oil was subjected to flash column chromatography (silica, 17:3 v/v PS 30-40/diethyl ether elution) to give two fractions, A and B.

Concentration of fraction **A** (R_f = 0.5 in 17:3 v/v hexane/ethyl acetate) yielded the title 3-benzosuberone **4.5** (169 mg, 28%) as a pale-yellow, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.3 in 17:3 v/v hexane/ethyl acetate) yielded methyl ester **4.65** (630 mg, 67% recovery) as a clear, pale-yellow oil. This material was identical, in all respects, with an authentic sample.

General Procedure A for the Horner-Wadsworth-Emmons (HWE) Reaction - Following a literature procedure,[7] a 50 mL Schlenk flask fitted with a very large stirrer bar was charged with a suspension of NaH (2.0 equiv., 60% dispersion in mineral oil) in THF and cooled to 0 °C. Trimethyl phosphonoacetate (2.0 equiv.) was added dropwise resulting in a thick white sludge. The reaction mixture was then stirred at room temperature for 0.5 h and subsequently cooled to 0 °C. A solution of ketone (1.0 equiv.) in THF was added slowly. After TLC analysis indicated complete consumption of the starting material the reaction was quenched by adding HCl (15 mL of a 1 M aq. solution), extracted with diethyl ether (2 x 10 mL), and the combined organic layers washed with brine (1 x 10 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was subjected to flash column chromatography.

(*EZ*)-Methyl 2-(2,3-dihydro-1*H*-inden-1-ylidene)acetate (4.66-*exo*) and Methyl 2-(1*H*-inden-3-yl)acetate (4.66-*endo*)



4.1 **4.66-*exo*** **4.66-*endo***

Following the general procedure A, a solution of 1-indanone (**4.1**) (0.26 mg, 2.0 mmol) in THF (10 mL) was added to a magnetically stirred slurry of NaH (0.16 g, 4.0 mmol, 60% dispersion in mineral oil) and trimethyl phosphonoacetate (0.65 mL, 4.0 mmol) in THF (8 mL) at room temperature, and stirring continued for 22 h. Flash column chromatography (silica, 4:1 v/v PS 30-40/diethyl ether elution) of the crude material yielded three fractions, A, B and C.

Concentration of fraction **A** (R_f = 0.6 in 17:3 v/v hexane/ethyl acetate) yielded the title exocyclic double bond isomer **4.66-*exo***[11] (12 mg, 3%) as a clear, colourless oil.

Compound 4.66-*exo*

^{1}H NMR (400 MHz) δ 8.83 (d, *J* = 7.9 Hz, 1H), 7.40 - 7.22 (complex m, 3H), 5.97 (s, 1H), 3.76 (s, 3H), 3.00 (m, 2H), 2.93 (m, 2H).

^{13}C NMR (100 MHz) δ 166.7 (CO), 160.9 (C), 151.0 (C), 137.5 (C), 130.8 (CH), 128.7 (CH), 126.6 (CH), 125.0 (CH), 110.3 (CH), 51.1 (CH_3), 35.7 (CH_2), 29.6 (CH_2).

IR ν_{max} 3067, 2947, 2847, 1715, 1630 cm^{-1}.

Concentration of fraction **B** (R_f = 0.5 in 17:3 v/v hexane/ethyl acetate) gave the title endocyclic double bond isomer **4.66-*endo***[11] (56 mg, 15%) as a colourless solid.

Compound 4.66-*endo*

^{1}H NMR (400 MHz) δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 3.8 Hz, 2H), 7.29 - 7.20 (complex m, 1H), 6.32 (t, *J* = 2.6 Hz, 1H), 3.77 (s, 3 H), 3.30 (m, 2H), 3.08 (t, *J* = 6.0 Hz, 2H).

^{13}C NMR (100 MHz) δ 168.0 (CO), 163.3 (C), 149.5 (C), 139.9 (C), 128.7 (CH), 126.7 (CH), 125.6 (CH), 121.6 (CH), 107.2 (CH), 51.0 (CH_3), 31.2 (CH_2), 30.6 (CH_2).

IR ν_{max} 3068, 2988, 2947, 2841, 1706, 1635 cm^{-1}.

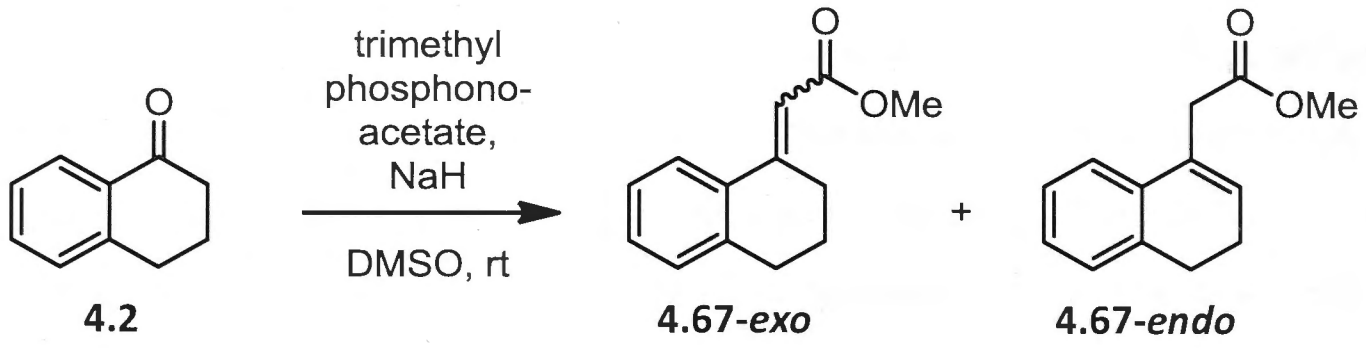
MS (EI, 70eV) *m/z* 188 ($M^{+\bullet}$, 93%), 157 (77), 129 (100), 128 (90), 77 (14).

HREIMS found: $M^{+\bullet}$, 188.0837, $C_{12}H_{12}O_2$ requires $M^{+\bullet}$ 188.0837.

mp 55-57 °C.

Concentration of fraction **C** (R_f = 0.3 in 17:3 v/v hexane/ethyl acetate) yielded 1-indanone (**4.1**) (0.18 g, 67% recovery) as a colourless solid. This material was identical, in all respects, with an authentic sample.

(*EZ*)-Methyl 2-(3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate (4.67-*exo*) and Methyl 2-(3,4-dihydronaphthalen-1-yl)acetate (4.67-*endo*)



4.2 **4.67-*exo*** **4.67-*endo***

A Schlenk flask fitted with a large stirrer bar was charged with a suspension of NaH (0.24 g, 6.0 mmol, 60% dispersion in mineral oil) in DMSO (3 mL) and cooled to 0 °C. Trimethyl phosphonoacetate (0.97 mL, 6.0 mmol) was added drop wise, resulting in a thick white sludge. The reaction mixture was stirred at room temperature for 0.5 h and subsequently re-cooled to 0 °C. A solution of 1-tetralone (**4.2**) (0.53 mL, 4.0 mmol) in DMSO (3 mL) was added slowly, and stirring continued at room temperature for 48 h, after which time the reaction was quenched with water (10 mL) and extracted with hexane (3 x 10 mL). The combined organic layers were washed with water (1 x 10 mL) and brine (1 x 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting pale-yellow oil was subjected to flash column chromatography (silica, 85:15 v/v PS 30-40/diethyl ether elution) to give three fractions, A, B and C.

Concentration of fraction **A** (R_f = 0.6 in 17:3 v/v hexane/ethyl acetate) yielded the title exocyclic double bond isomer **4.67-*exo***[12] (0.032 g, 4%) as a clear, colourless oil.

Compound 4.67-*exo*

^{1}H NMR (400 MHz) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.35 (s, 1H), 3.75 (s, 3H), 3.21 (t, *J* = 6.1 Hz, 2H), 2.80 (t, *J* = 6.1 Hz, 2H), 1.86 (quintet, *J* = 6.3 Hz, 2H).

^{13}C NMR (100 MHz) δ 167.4 (CO), 155.0 (C), 140.3 (C), 134.1 (C), 129.5 (CH), 129.1 (CH), 126.3 (CH), 124.7 (CH), 111.5 (CH), 50.9 (CH_3), 30.1 (CH_2), 28.0 (CH_2), 22.6 (CH_2).

Concentration of fraction **B** (R_f = 0.5 in 17:3 v/v hexane/ethyl acetate) gave the endocyclic double bond isomer **4.67-*endo***[12] (0.15 g, 19%) as a clear, colourless oil.

Compound 4.67-*endo*

^{1}H NMR (400 MHz) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 2H), 5.92 (s, 1H), 3.80 (s, 3H), 2.97 (t, *J* = 6.6 Hz, 2H), 2.62 (t, *J* = 6.5 Hz, 2H), 2.08 (quintet, *J* = 6.6 Hz, 2H).

^{13}C NMR (100 MHz) δ 167.3 (CO), 153.1 (C), 138.9 (C), 133.0 (C), 129.3 (CH), 129.2 (CH), 128.3 (CH), 124.6 (CH), 113.5 (CH), 50.0 (CH_3), 34.9 (CH_2), 29.0 (CH_2), 23.0 (CH_2).

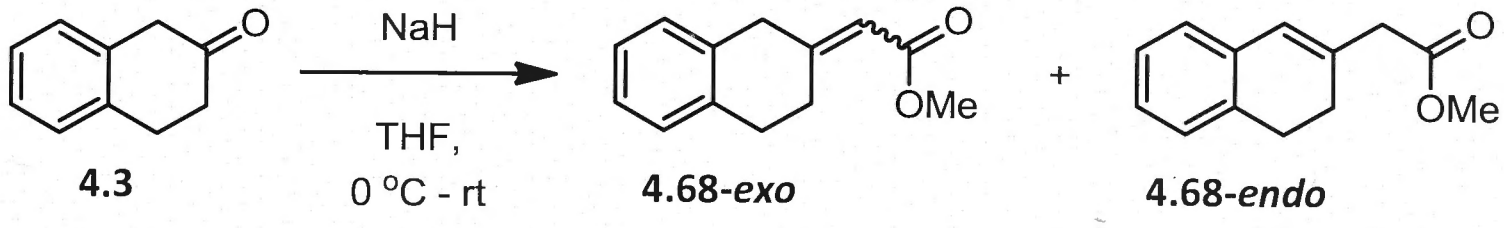
IR ν_{max} 3065, 2924, 2853, 1716, 1621 cm^{-1}.

MS (EI, 70eV) *m/z* 202 ($M^{+\bullet}$, 100%), 171 (55), 143 (50), 128 (65), 115 (40).

HREIMS found: $M^{+\bullet}$, 202.0993. $C_{13}H_{14}O_2$ requires $M^{+\bullet}$, 202.0994.

Concentration of fraction **C** (R_f = 0.4 in 17:3 v/v hexane/ethyl acetate) yielded 1-tetralone (**4.2**) (382 mg, 65% recovery) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample.

(*EZ*)-Methyl 2-(3,4-dihydronaphthalen-2(1*H*)-ylidene)acetate (4.68-*exo*) and Methyl 2-(3,4-dihydronaphthalen-2-yl)acetate (4.68-*endo*)



4.3 **4.68-*exo*** **4.68-*endo***

Following general procedure A, a magnetically stirred mixture of NaH (0.32 g, 8.0 mmol, 60% dispersion in mineral oil) and trimethyl phosphonoacetate (1.3 mL, 8.0 mmol) in THF (10 mL) maintained at room temperature was treated with a solution of 2-tetralone (**4.3**) (0.64 g, 0.60 mL, 4.0 mmol) in THF (10 mL) and stirring continued for 1.5 h. Flash column chromatography (silica, 3:1 v/v PS 30-40/diethyl ether elution) of the crude material yielded two fractions, A and B.

Concentration of fraction **A** (R_f = 0.5 in 17:3 v/v hexane/ethyl acetate) yielded the title exocyclic double bond isomer **4.68-*exo***[12] (5 mg, 1%) as a clear, colourless oil.

Compound 4.68-*exo*

^{1}H NMR (400 MHz) δ 7.19 - 7.08 (complex m, 4H), 5.87 (s, 1H), 3.70 (s, 3H), 3.57 (s, 2H), 3.11 (t, *J* = 3.1 Hz, 2H), 2.86 (t, *J* = 2.8 Hz, 2H).

^{13}C NMR (100 MHz) δ 166.9 (CO), 160.2 (C), 137.9 (C), 135.2 (C), 127.5 (CH), 127.4 (CH), 126.4 (CH), 126.3 (CH), 113.9 (CH), 50.9 (CH_3), 39.8 (CH_2), 29.1 (CH_2), 28.3 (CH_2).

IR ν_{max} 3065, 3021, 2947, 2844, 1716, 1646 cm^{-1}.

MS (EI, 70eV) *m/z* 202 ($M^{+\bullet}$, 50%), 143 (50), 128 (100), 115 (20).

HREIMS found: $M^{+\bullet}$, 202.0998. $C_{13}H_{14}O_2$ requires $M^{+\bullet}$, 202.0994.

Concentration of fraction **B** (R_f = 0.4 in 17:3 v/v hexane/ethyl acetate) gave the endocyclic double bond isomer **4.68-*endo***[12] (0.77 g, 95%) as a clear, colourless oil.

Compound 4.68-*endo*

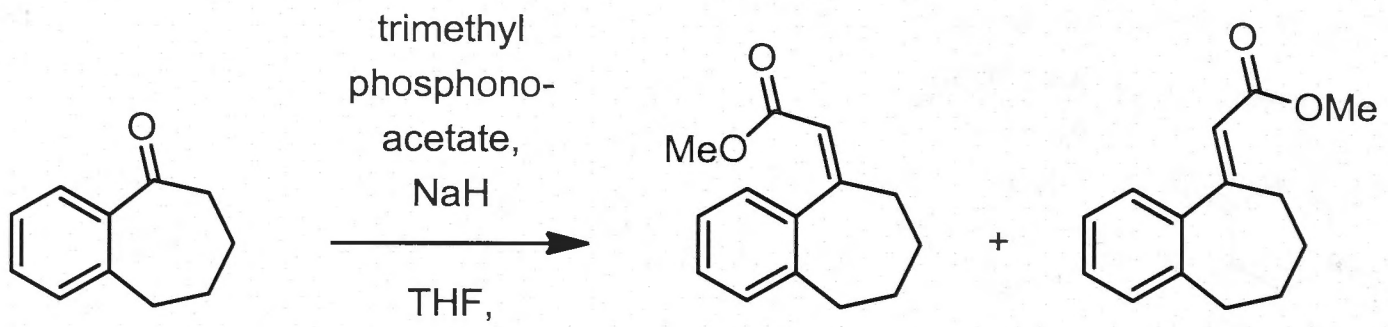
^{1}H NMR (400 MHz) δ 7.18 - 7.03 (m, 3H), 7.00 (d, *J* = 6.2 Hz, 1H), 6.35 (s, 1H), 3.71 (s, 3H), 3.22 (s, 2H), 2.85 (t, *J* = 2.8 Hz, 2H), 2.35 (t, *J* = 2.3 Hz, 2H).

^{13}C NMR (125 MHz) δ 171.6 (CO), 134.4 (C), 134.1 (C), 133.7 (C), 127.2 (CH), 126.8 (CH), 126.4 (CH), 126.2 (CH), 125.8 (CH), 51.9 (CH_3), 42.7 (CH_2), 27.9 (CH_2), 27.2 (CH_2).

IR ν_{max} 3021, 2924, 2853, 1719, 1647 cm^{-1}.

MS (EI, 70eV) *m/z* 202 ($M^{+\bullet}$, 30%), 142 (50), 128 (100), 115 (20).

(*Z*)-Methyl 2-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene)acetate (4.69-*Z*) and (*E*)-Methyl 2-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene)acetate (4.69-*E*)



4.4 **4.69-*Z*** **4.69-*E***

Following general procedure A, a solution of 1-benzosuberone (**4.4**) (0.32 mg, 2.0 mmol) in THF (10 mL) was added to a magnetically stirred mixture of NaH (0.16 g, 4.0 mmol, 60% dispersion in mineral oil) and trimethyl phosphonoacetate (0.65 mL, 4.0 mmol) in THF (8 mL) at room temperature and stirring continued for 22 h. Flash column chromatography (silica, 19:1 v/v PS 30-40/diethyl ether elution) of the crude material yielded, after concentration of the appropriate fractions, three compounds.

Concentration of fraction **A** (R_f = 0.7 in 17:3 v/v hexane/ethyl acetate) yielded the title *Z*-isomer **4.69-*Z***[13] (0.025 g, 6%) as a clear, colourless oil.

Compound 4.69-*Z*

^{1}H NMR (400 MHz) δ 7.18 - 7.08 (complex m, 3H), 7.12 (d, *J* = 7.0 Hz, 1H), 5.89 (s, 1H), 3.70 (s, 3H), 3.75 (s, 3H), 3.00 (s, 2H), 2.75 (t, *J* = 5.7 Hz, 2H), 1.79 (m, 2H).

^{13}C NMR (100 MHz) δ 166.9 (CO), 164.5 (C), 143.0 (C), 139.5 (C), 129.0 (CH), 128.4 (CH), 127.0 (CH), 127.3 (CH), 117.2 (CH), 51.0 (CH_3), 34.1 (CH_2), 31.2 (CH_2), 26.9 (CH_2).

IR ν_{max} 3062, 30116, 2931, 2858, 1716, 1632 cm^{-1}.

MS (EI, 70eV) *m/z* 216 ($M^{+\bullet}$, 100%), 185 (50), 156 (40), 128 (75), 117 (45).

Concentration of fraction **B** (R_f = 0.6 in 17:3 v/v hexane/ethyl acetate) gave the title *E*-isomer **4.69-*E***[13] (0.12 g, 27%) as a clear, colourless oil.

Compound 4.69-*E*

^{1}H NMR (400 MHz) δ 7.22 - 7.12 (complex m, 3H), 7.05 (d, *J* = 6.7 Hz, 1H), 6.97 (s, 1H), 3.54 (s, 3H), 2.74 (m, 2H), 2.40 (t, *J* = 5.9 Hz, 2H), 1.92 (m, 2H), 1.74 (m, 2H).

^{13}C NMR (100 MHz) δ 166.3 (CO), 162.9 (C), 141.0 (C), 138.9 (C), 128.9 (CH), 127.7 (CH), 127.7 (CH), 125.5 (CH), 116.8 (CH), 51.0 (CH_3), 38.7 (CH_2), 35.9 (CH_2), 32.5 (CH_2), 27.6 (CH_2).

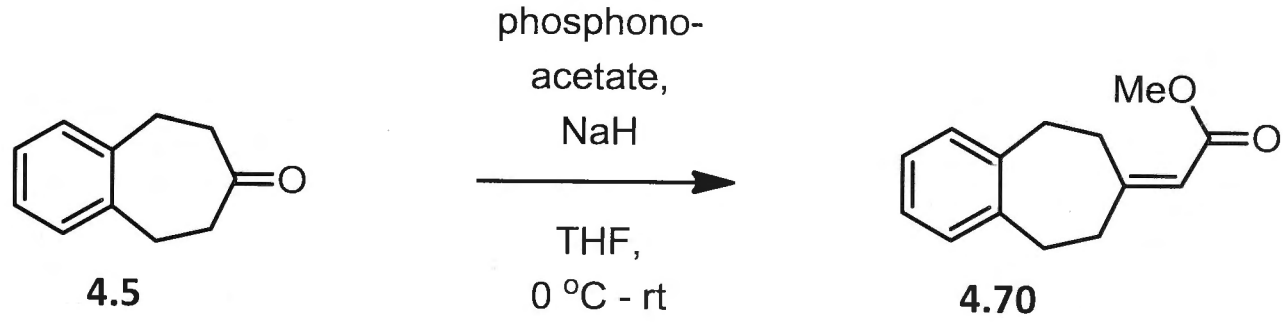
IR ν_{max} 3018, 2929, 2851, 1727, 1676 cm^{-1}.

MS (EI, 70eV) *m/z* 216 ($M^{+\bullet}$, 100%), 185 (45), 128 (65), 117 (45).

HREIMS found: $M^{+\bullet}$, 216.1153. $C_{14}H_{16}O_2$ requires $M^{+\bullet}$, 216.1150.

Concentration of fraction **C** (R_f = 0.5 in 17:3 v/v hexane/ethyl acetate) yielded 1-benzosuberone (**4.4**) (0.22 g, 50% recovery) as a colourless oil. This material was identical, in all respects, with an authentic sample.

Methyl 2-(8,9-dihydro-5*H*-benzo[7]annulen-7(6*H*)-ylidene)acetate (4.70)



4.5 **4.70**

Following general procedure A, a solution of 3-benzosuberone (**4.5**) (0.70 mg, 4.4 mmol) in THF (10 mL) was added to a magnetically stirred mixture of NaH (0.29 g, 6.5 mmol, 60% dispersion in mineral oil) and trimethyl phosphonoacetate (1.1 mL, 6.5 mmol) in THF (25 mL) at room temperature and stirring continued for 22 h. Flash column chromatography (silica, 9:1 v/v PS 30-40/diethyl ether elution) of the crude material yielded, after concentration of the appropriate fractions (R_f = 0.7, 17:3 v/v hexane/ethyl acetate), the title methyl ester **4.70** (0.93 g, 98%) as a colourless solid.

^{1}H NMR (300 MHz) δ 7.15 (m, 4H), 5.71 (s, 1H), 3.71 (s, 3H), 3.03 (t, *J* = 5.5 Hz, 2H), 2.86 (m, 4H), 2.40 (t, *J* = 5.5 Hz, 2H).

^{13}C NMR (75 MHz) δ 164.8 (CO), 142.2 (C), 141.4 (C), 129.2 (CH), 129.1 (CH), 126.5 (CH), 126.4 (CH), 114.9 (CH), 51.0 (CH_3), 39.9 (CH_2), 35.3 (CH_2), 34.4 (CH_2), 31.2 (CH_2).

IR ν_{max} 3017, 2945, 2849, 1716, 1643 cm^{-1}.

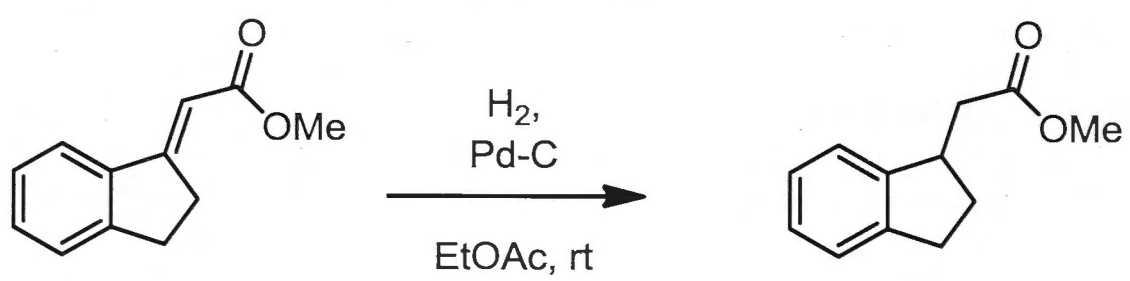
MS (EI, 70eV) *m/z* 216 ($M^{+\bullet}$, 100%), 157 (40), 142 (40), 129 (45), 115 (30), 91 (20).

HREIMS found: $M^{+\bullet}$, 216.1145. $C_{14}H_{16}O_2$ requires $M^{+\bullet}$, 216.1150.

mp 80-81 °C.

General Procedure B for the Hydrogenation - A solution of α,β-unsaturated ester (1 equiv.) in ethyl acetate was treated with 10% palladium on carbon (5-6 mol%). The flask was evacuated and refilled with hydrogen gas three times and the reaction mixture stirred vigorously at room temperature for 1 h. The flask was then flushed with nitrogen and the reaction mixture filtered through Celite™ and the filtrate concentrated under reduced pressure to yield the corresponding saturated ester.

Methyl 2-(2,3-dihydro-1*H*-inden-1-yl)acetate (4.71)



4.66 **4.71**

Following general procedure B, a solution of α,β-unsaturated esters **4.66-endo/-exo** (120 mg, 0.638 mmol) in ethyl acetate (5 mL), was treated with 10% palladium on carbon (41 mg, 6 mol%) under an atmosphere of hydrogen gas at room temperature. After 1 h the reaction mixture was filtered through Celite™ and the filtrate concentrated under reduced pressure to yield the *title ester* ***4.71*** (121 mg, 99%) as a clear, colourless oil. The crude product was used without further purification in the next step of the reaction sequence.

^{1}H NMR (400 MHz) δ 7.23 (m, 1H), 7.17 (m, 3H), 3.74 (s, 3H), 3.61 (quintet, *J* = 7.5 Hz, 1H), 2.92 (m, 2H), 2.80 (dd, *J* = 15.7, 6.0 Hz, 1H), 2.46 (dd, *J* = 16.1, 9.3 Hz, 1H), 2.40 (m, 1H), 1.76 (m, 1H).

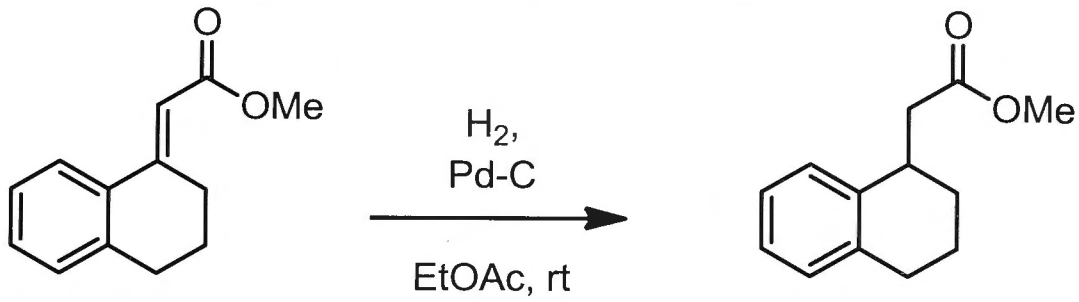
^{13}C NMR (100 MHz) δ 173.2 (CO), 145.6 (C), 143.8 (C), 126.7 (CH), 126.2 (CH), 124.6 (CH), 123.4 (CH), 51.6 (CH_3), 41.3 (CH), 39.6 (CH_2), 32.4 (CH_2), 31.1 (CH_2).

IR ν_{max} 3069, 3020, 2950, 2847, 1738 cm^{-1}.

MS (EI, 70eV) *m/z* 190 ($M^{+\bullet}$, 30%), 130 (40), 117 (100), 91 (15).

HREIMS found: $M^{+\bullet}$, 190.1000. $C_{12}H_{14}O_2$ requires $M^{+\bullet}$, 190.0994.

Methyl 2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetate (4.72)



4.67 **4.72**

Following general procedure B, a solution of α,β-unsaturated esters **4.67-*endo*/-*exo*** (205 mg, 1.01 mmol) in ethyl acetate (5 mL) was treated with 10% palladium on carbon (66 mg, 6 mol%) under an atmosphere of hydrogen gas at room temperature. After 1 h the reaction mixture was filtered through Celite™ and the filtrate concentrated under reduced pressure. The resulting pale-yellow oil was subjected to flash column chromatography (silica, 9:1 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.7 in 17:3 v/v hexane/ethyl acetate), the *title ester* ***4.72*** (43 mg, 23%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 7.19 - 7.06 (complex m, 4H), 3.72 (s, 3H), 3.37 (m, 1H), 2.78 (m, 2H), 2.74 (dd, *J* = 15.6, 5.3 Hz, 1H), 2.57 (dd, *J* = 14.8, 9.5 Hz, 1H), 1.98 - 1.67 (complex m, 4H).

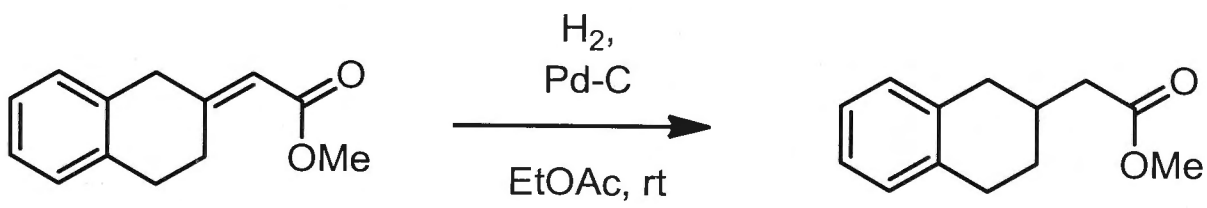
^{13}C NMR (100 MHz) δ 173.2 (CO), 139.2 (C), 137.1 (C), 129.2 (CH), 128.2 (CH), 126.0 (CH), 125.8 (CH), 51.5 (CH_3), 41.8 (CH), 34.5 (CH_2), 29.5 (CH_2), 28.1 (CH_2), 19.4 (CH_2).

IR ν_{max} 3060, 3017, 2924, 2854, 1742 cm^{-1}.

MS (EI, 70eV) *m/z* 204 ($M^{+\bullet}$, 30%), 144 (60), 131 (100), 130 (80), 115 (20).

HREIMS found: $M^{+\bullet}$, 204.1146. $C_{13}H_{16}O_2$ requires $M^{+\bullet}$, 204.1150.

Methyl 2-(1,2,3,4-tetrahydronaphthalen-2-yl)acetate (4.73)



4.68 **4.73**

Following general procedure B, a solution of α,β-unsaturated esters **4.68-*endo*/-*exo*** (950 mg, 4.70 mmol) in ethyl acetate (25 mL) was treated with 10% palladium on carbon (300 mg, 6 mol%) under an atmosphere of hydrogen gas at room temperature. After 1 h the reaction mixture was filtered through Celite™ and the filtrate concentrated under reduced pressure. The resulting pale yellow oil was subjected to flash column chromatography (silica, 90:10 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 17:3 v/v hexane/ethyl acetate), the *title ester* ***4.73*** (793 mg, 83%) as a colourless solid.

^{1}H NMR (400 MHz) δ 7.14 - 7.03 (complex m, 4H), 3.72 (s, 3H), 2.91 (dd, *J* = 16.3, 4.9 Hz, 1H), 2.85 (dd, *J* = 8.5, 5.0 Hz, 2H), 2.52 (dd, *J* = 16.4, 10.5 Hz, 2H), 2.40 (d, *J* = 7.6 Hz, 2H), 2.36 - 2.19 (complex m, 1H), 2.02 - 1.92 (complex m, 1H), 1.53 - 1.42 (complex m, 1H).

^{13}C NMR (100 MHz) δ 173.2 (CO), 136.1 (C), 135.7 (C), 129.1 (CH), 128.8 (CH), 125.7 (CH), 125.6 (CH), 51.5 (CH_3), 40.8 (CH), 35.6 (CH_2), 31.3 (CH_2), 29.1 (CH_2), 28.7 (CH_2).

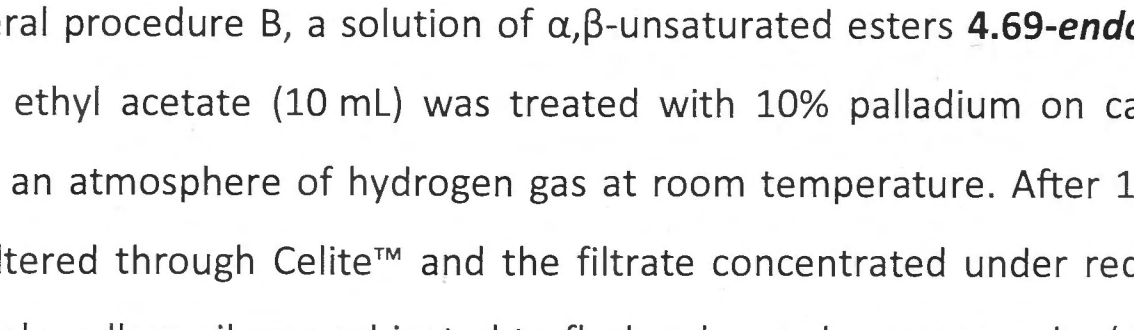
IR ν_{max} 3061, 3018, 2919, 2842, 1738 cm^{-1}.

MS (EI, 70eV) *m/z* 204 ($M^{+\bullet}$, 30%), 172 (15), 131 (30), 130 (100), 115 (20).

HREIMS found: $M^{+\bullet}$, 204.1151. $C_{13}H_{16}O_2$ requires $M^{+\bullet}$, 204.1150.

mp 43-44 °C.

Methyl 2-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)acetate (4.74)



4.69 **4.74**

Following general procedure B, a solution of α,β-unsaturated esters **4.69-*endo*/-*exo*** (350 mg, 1.62 mmol) in ethyl acetate (10 mL) was treated with 10% palladium on carbon (103 mg, 6 mol%) under an atmosphere of hydrogen gas at room temperature. After 1 h the reaction mixture was filtered through Celite™ and the filtrate concentrated under reduced pressure. The resulting pale-yellow oil was subjected to flash column chromatography (silica, 9:1 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 17:3 v/v hexane/ethyl acetate), the *title ester* ***4.74*** (320 mg, 91%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 7.11 (m, 4H), 3.68 (s, 3H), 3.49 (q, *J* = 8.5 Hz, 1H), 2.90 (q, *J* = 10.0 Hz, 1H), 2.83 (covered, 1H), 2.83 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.73 (dd, *J* = 15.0, 8.5 Hz, 1H), 1.95 - 1.68 (complex m, 4H), 1.67 - 1.48 (complex m, 2H).

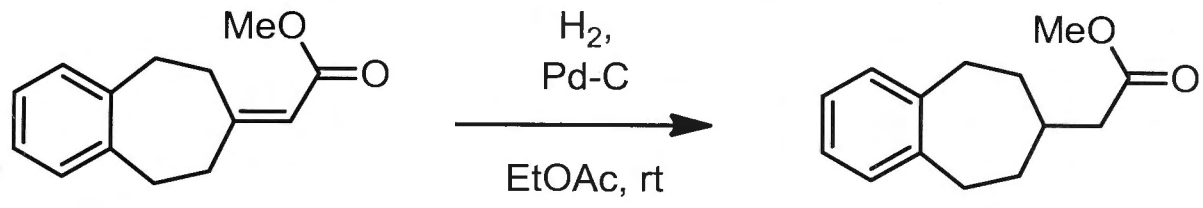
^{13}C NMR (100 MHz) δ 173.3 (CO), 143.8 (C), 142.6 (C), 129.8 (CH), 126.3 (CH), 126.1 (2 x CH), 51.6 (CH_3), 40.7 (CH), 38.3 (CH_2), 36.0 (CH_2), 33.3 (CH_2), 29.0 (CH_2), 27.8 (CH_2).

IR ν_{max} 3062, 3018, 2921, 2850, 1739 cm^{-1}.

MS (EI, 70eV) *m/z* 218 ($M^{+\bullet}$, 40%), 158 (40), 145 (100), 143 (70).

HREIMS found: $M^{+\bullet}$, 218.1312. $C_{14}H_{18}O_2$ requires $M^{+\bullet}$, 218.1307.

Methyl 2-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)acetate (4.75)



4.70 **4.75**

Following general procedure B, a solution of α,β-unsaturated esters **4.70-endo/-exo** (1.15 g, 5.32 mmol) in ethyl acetate (25 mL) was treated with 10% palladium on carbon (340 mg, 6 mol%) under an atmosphere of hydrogen gas at room temperature. After 2 h the reaction mixture was filtered through Celite™ and the filtrate concentrated under reduced pressure to give the *title ester* ***4.75*** (786 mg, 68%) as a colourless solid. The crude product was used without further purification in the next step of the reaction sequence.

^{1}H NMR (400 MHz) δ 7.10 (s, 4H), 3.69 (s, 3H), 2.86 (ddd, *J* = 14.4, 11.4, 1.8 Hz, 2H), 2.76 (ddd, *J* = 14.4, 7.1, 1.8 Hz, 2H), 2.24 (m, 2H), 2.21 (covered, 1H), 2.00 - 1.92 (complex m, 2H), 1.16 (m, 2H).

^{13}C NMR (100 MHz) δ 173.3 (CO), 142.7 (C), 128.8 (CH), 126.1 (CH), 51.5 (CH_3), 42.3 (CH), 40.2 (CH_2), 34.7 (CH_2), 34.0 (CH_2).

IR ν_{max} 3061, 3019, 2914, 2850, 1729 cm^{-1}.

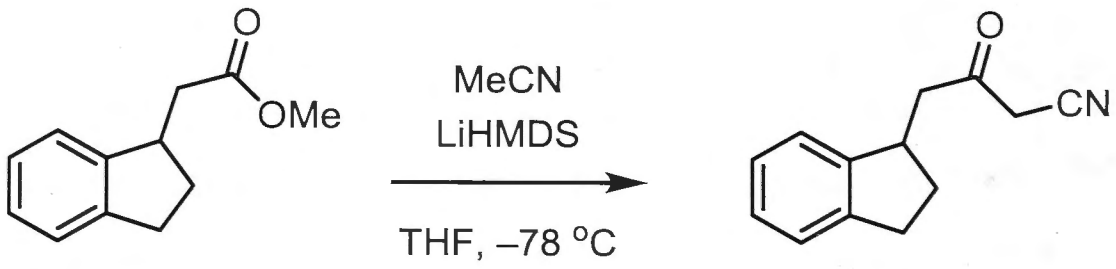
MS (EI, 70eV) *m/z* 218 ($M^{+\bullet}$, 70%), 186 (80), 143 (80), 129 (100), 84 (90).

HREIMS found: $M^{+\bullet}$, 218.1297. $C_{14}H_{18}O_2$ requires $M^{+\bullet}$, 218.1307.

mp 62-64 °C.

General Procedure C for the Formation of* β-*Ketonitriles - A magnetically stirred solution of LiHMDS (1.4 equiv., 1 M soln. in THF) in THF was treated with acetonitrile (1.2 equiv.) at −78 °C drop wise. After stirring at this temperature for 1 h, a solution of methyl ester (1 equiv.) in THF was added slowly. The reaction mixture was allowed to warm to room temperature slowly, and diluted with diethyl ether. HCl (1 M aq. solution) was added until the mixture became clear, followed by addition of brine (10 mL). The separated aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers washed with brine (1 x 10 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude β-ketonitrile was subjected to flash column chromatography.

4-(2,3-Dihydro-1*H*-inden-1-yl)-3-oxobutanenitrile (4.76)



4.71 **4.76**

Following general procedure C, a solution of LiHMDS (1.4 mL, 1 M soln. in THF) in THF (3 mL) was treated with acetonitrile (43 µl, 0.82 mmol) at −78°C drop wise. After 1 h a solution of the ester **4.71** (130 mg, 0.683 mmol) in THF (3 mL) was added slowly and stirring continued for 16 h, during which time it was allowed to warm to room temperature. Flash column chromatography (silica, 2:3 v/v PS 30-40/diethyl ether elution) of the crude material yielded, after concentration of the appropriate fractions (R_f = 0.2 in 17:3 v/v hexane/ethyl acetate) the *title β-ketonitrile* ***4.76*** (125 mg, 92%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz) δ 7.19 (m, 4H), 3.66 (m, 1H), 3.47 (s, 2H), 3.08 (dd, *J* = 17.4, 5.4 Hz, 1H), 2.92 (m, 1H), 2.79 (dd, *J* = 17.4, 8.4 Hz, 1H), 2.43 (m, 1H), 1.67 (m, 1H).

^{13}C NMR (100 MHz) δ 196.7 (CO), 144.8 (C), 143.7 (C), 127.1 (CH), 126.5 (CH), 124.8 (CH), 123.3 (CH), 113.6 (CN), 47.8 (CH_2), 39.9 (CH_2), 32.4 (CH), 32.3 (CH_2), 31.2 (CH_2).

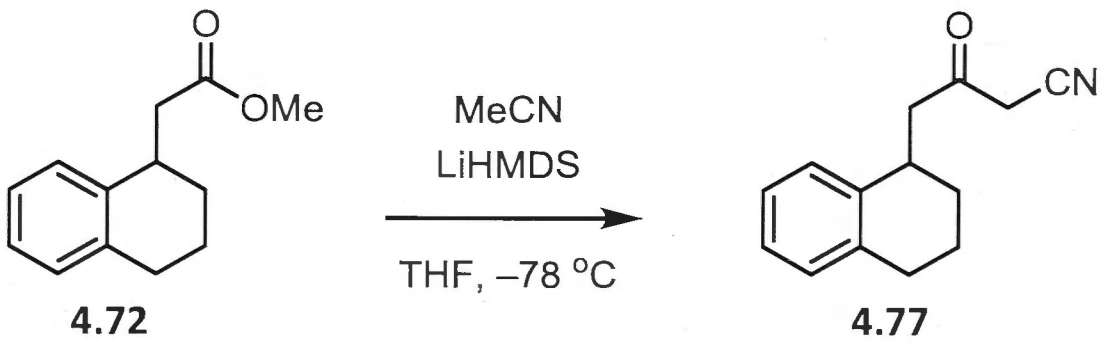
IR ν_{max} 3068, 3021, 2918, 2260, 1731 cm^{-1}.

MS (EI, 70eV) *m/z* 199 ($M^{+\bullet}$, 45%), 159 (15), 130 (15), 117 (100).

HREIMS found: $M^{+\bullet}$, 199.1001. $C_{13}H_{13}NO$ requires $M^{+\bullet}$, 199.0997.

mp 40-41 °C.

3-Oxo-4-(1,2,3,4-tetrahydronaphthalen-1-yl)butanenitrile (4.77)



4.72 **4.77**

Following general procedure C, a solution of LiHMDS (0.42 mL, 1 M soln. in THF) in THF (1 mL) was treated with acetonitrile (13 µl, 0.25 mmol) at −78°C drop wise. After 1 h a solution of ester **4.72** (43 mg, 0.21 mmol) in THF (1 mL) was added slowly and stirring continued for 16 h. Flash column chromatography (silica, 2:3 v/v PS 30-40/diethyl ether elution) of the crude material yielded, after concentration of the appropriate fractions (R_f = 0.2 in 17:3 v/v hexane/ethyl acetate) the *title β-ketonitrile* ***4.77*** (30 mg, 67%) as a pale-yellow wax.

^{1}H NMR (400 MHz) δ 7.11 (m, 4H), 3.47 (m, 1H), 3.44 (s, 2H), 2.94 (m, 2H), 2.78 (m, 1H), 1.94 (sextet, *J* = 5.7 Hz, 1H), 1.79 (quintet, *J* = 5.9 Hz, 2H), 1.68 - 1.60 (complex m, 1H).

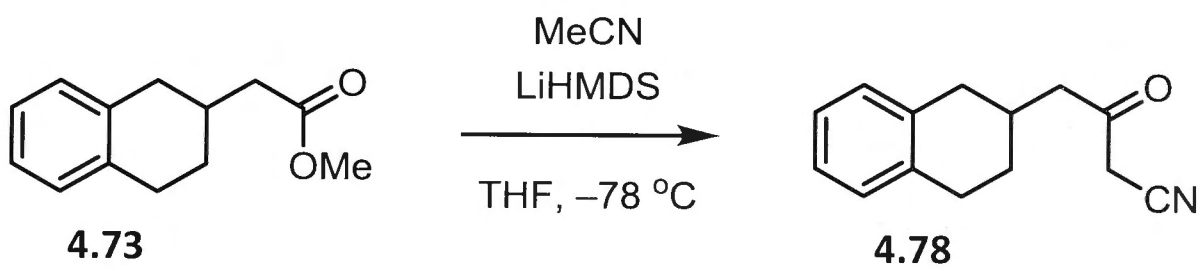
^{13}C NMR (125 MHz) δ 196.7 (CO), 138.5 (C), 137.1 (C), 129.5 (CH), 128.1 (CH), 126.3 (CH), 126.0 (CH), 113.6 (CN), 49.7 (CH_2), 33.1 (CH), 32.6 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 19.5 (CH_2).

IR ν_{max} 3060, 3017, 2930, 2259, 1730 cm^{-1}.

MS (EI, 70eV) *m/z* 213 ($M^{+\bullet}$, 15%), 145 (15), 131 (100), 115 (25).

HREIMS found: $M^{+\bullet}$, 213.1160. $C_{14}H_{15}NO$ requires $M^{+\bullet}$, 213.1154.

3-Oxo-4-(1,2,3,4-tetrahydronaphthalen-2-yl)butanenitrile (4.78)



4.73 **4.78**

Following general procedure C, a magnetically stirred solution of LiHMDS (4.9 mL, 1 M soln. in THF) in THF (4 mL) was treated with acetonitrile (0.15 mL, 2.9 mmol) at −78°C drop wise. After 1 h a solution of ester **4.73** (500 mg, 2.45 mmol) in THF (4 mL) was added slowly and stirring continued for 16 h, during which time it was allowed to warm to room temperature. Flash column chromatography (silica, 1:1 v/v PS 30-40/diethyl ether elution) of the crude material yielded, after concentration of the appropriate fractions (R_f = 0.1 in 17:3 v/v hexane/ethyl acetate), the *title β-ketonitrile* ***4.78*** (345 mg, 66%) as a pale-yellow solid.

^{1}H NMR (400 MHz) δ 7.08 (m, 4H), 3.49 (s, 2H), 2.95 - 2.81 (complex m, 3H), 2.68 (d, *J* = 6.4 Hz, 2H), 2.48 (dd, *J* = 16.0, 10.2 Hz, 1H), 2.38 (m, 1H), 2.00 - 1.89 (complex m, 1H), 1.49 (m, 1H).

^{13}C NMR (100 MHz) δ 196.7 (CO), 138.8 (C), 135.1 (C), 129.0 (CH), 128.9 (CH), 125.9 (CH), 125.7 (CH), 113.7 (CN), 48.3 (CH_2), 35.3 (CH), 32.4 (CH_2), 29.8 (CH_2), 28.9 (CH_2), 28.4 (CH_2).

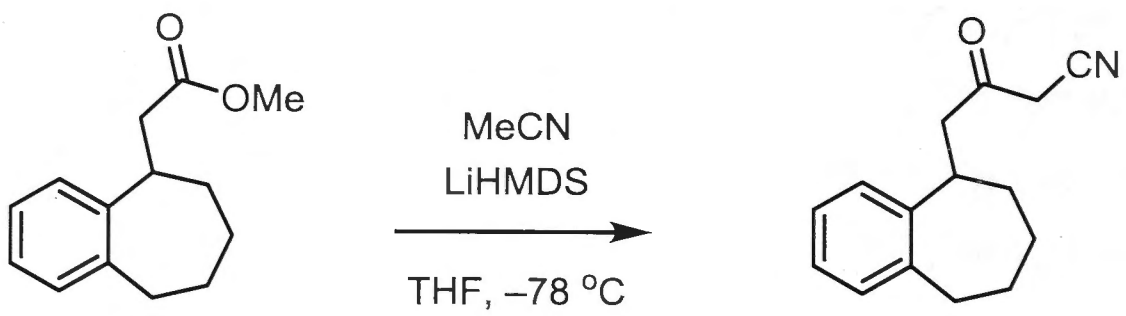
IR ν_{max} 3060, 3017, 2918, 2261, 1731 cm^{-1}.

MS (EI, 70eV) *m/z* 213 ($M^{+\bullet}$, 5%), 143 (5), 130 (100), 115 (15).

HREIMS found: $M^{+\bullet}$, 213.1154. $C_{14}H_{15}NO$ requires $M^{+\bullet}$, 213.1154.

mp 54-56 °C.

3-Oxo-4-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)butanenitrile (4.79)



4.74 **4.79**

Following general procedure C, a solution of LiHMDS (3.2 mL, 1 M soln. in THF) in THF (3 mL) was treated with acetonitrile (100 µl, 1.94 mmol) at −78°C drop wise. After 1 h a solution of ester **4.74** (353 mg, 1.62 mmol) in THF (3 mL) was added slowly and stirring continued for 16 h, during which time it was allowed to warm to room temperature. Flash column chromatography (silica, 1:1 v/v PS 30-40/diethyl ether elution) of the crude material yielded two fractions, A and B.

Concentration of fraction **A** (R_f = 0.6 in 17:3 v/v hexane/ethyl acetate) yielded compound **4.74** (141 mg, 40% recovery) as a pale-yellow oil. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.2 in 17:3 v/v hexane/ethyl acetate) yielded the *title β-ketonitrile* ***4.79*** (148 mg, 40%) as an off-white solid.

Compound 4.79

^{1}H NMR (400 MHz) δ 7.12 (m, 3H), 7.04 (m, 1H), 3.53 (dq, *J* = 7.4, 2.2 Hz, 1H), 3.36 (d, *J* = 2.8 Hz, 2H), 3.15 (dd, *J* = 16.8, 6.7 Hz, 1H), 2.97 (dd, *J* = 16.8, 7.3 Hz, 1H), 2.87 (m, 2H), 1.83 (m, 2H), 1.72 (m, 2H), 1.66 (m, 2H).

^{13}C NMR (10 MHz) δ 196.7 (CO), 142.8 (C), 142.4 (C), 130.2 (CH), 126.7 (CH), 126.3 (CH), 113.6 (CN), 45.7 (CH_2), 39.8 (CH), 36.1 (CH_2), 33.3 (CH_2), 32.5 (CH_2), 28.6 (CH_2), 27.7 (CH_2).

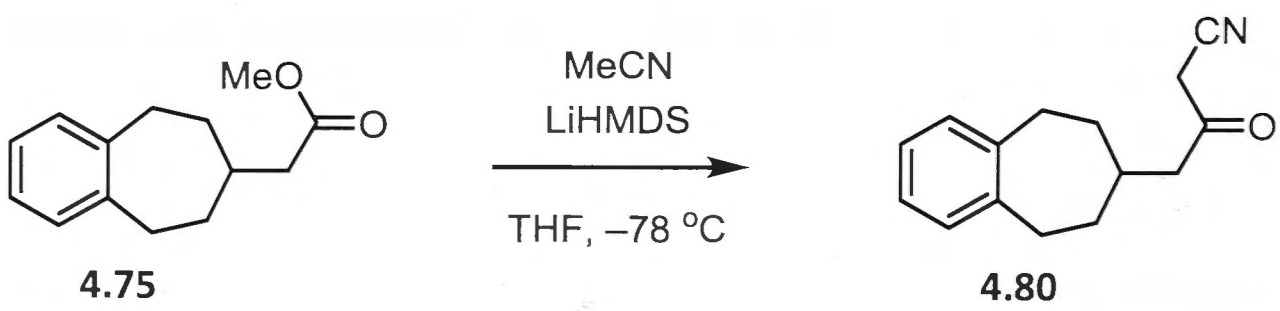
IR ν_{max} 3060, 3019, 2922, 2852, 2259, 1729 cm^{-1}.

MS (EI, 70eV) *m/z* 227 ($M^{+\bullet}$, 25%), 187 (20), 145 (100), 129 (30), 117 (30).

HREIMS found: $M^{+\bullet}$, 227.1309. $C_{15}H_{17}NO$ requires $M^{+\bullet}$, 227.1310.

mp 93-95 °C.

3-Oxo-4-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)butanenitrile (4.80)



4.75 **4.80**

Following general procedure C, a solution of LiHMDS (4.6 mL, 1 M soln. in THF) in THF (4 mL) was treated with acetonitrile (140 µl, 2.75 mmol) at −78°C drop wise. After 1 h a solution of the ester **4.75** (500 mg, 2.29 mmol) in THF (4 mL) was added slowly and stirring continued for 16 h, during which time it was allowed to warm to room temperature. Flash column chromatography (silica, 1:1 v/v PS 30-40/diethyl ether elution) of the crude material yielded two fractions, A and B.

Concentration of fraction **A** (R_f = 0.6 in 17:3 v/v hexane/ethyl acetate) yielded compound **4.75** (107 mg, 21% recovery) as a pale-yellow oil. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.1 in 17:3 v/v hexane/ethyl acetate) yielded the *title β-ketonitrile* ***4.80*** (328 mg, 63%) as an off-white solid.

Compound 4.80

^{1}H NMR (400 MHz) δ 7.10 (m, 4H), 3.43 (s, 2H), 2.87 (dd, *J* = 14.0, 12.2 Hz, 2H), 2.76 (ddd, *J* = 14.0, 7.3, 1.5 Hz, 2H), 2.53 (d, *J* = 6.7 Hz, 2H), 2.32 (m, 1H), 1.92 (m, 2H), 1.16 (q, *J* = 11.8 Hz, 2H).

^{13}C NMR (100 MHz) δ 196.7 (CO), 142.4 (C), 128.9 (CH), 113.6 (CN), 49.9 (CH_2), 38.7 (CH), 34.6 (CH_2), 34.0 (CH_2), 32.5 (CH_2).

IR ν_{max} 3065, 3019, 2921, 2848, 2261, 1722 cm^{-1}.

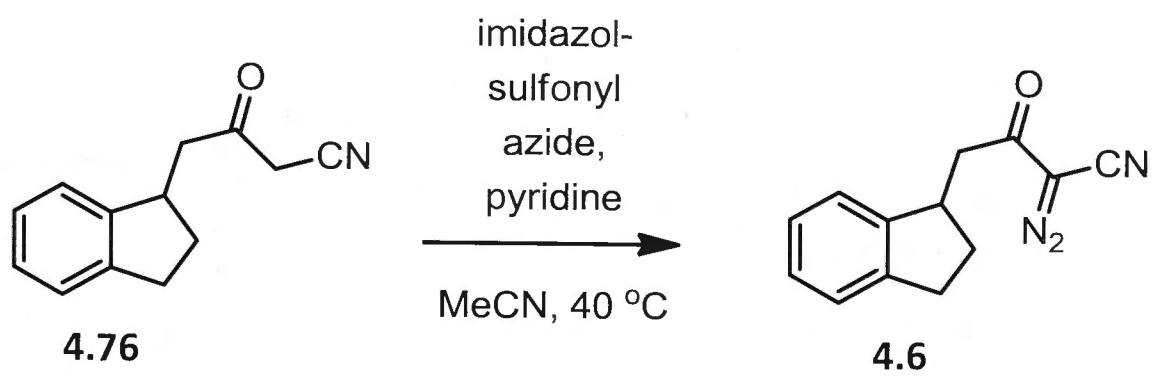
MS (EI, 70eV) *m/z* 227 ($M^{+\bullet}$, 60%), 209 (30), 143 (55), 129 (100), 117 (40).

HREIMS found: $M^{+\bullet}$, 227.1309. $C_{15}H_{17}NO$ requires $M^{+\bullet}$, 227.1310.

mp 116-121 °C.

General Procedure D for the Diazo-Transfer Reaction – Freshly prepared imidazolesulfonyl azide[14] (1.3 equiv.) (CAUTION – this compound is potentially explosive) was added to a magnetically stirred solution of β-ketonitrile (1 equiv.) in MeCN. The reaction mixture was heated at 40 °C and treated with pyridine (5 equiv.). After the specified time (overnight) the reaction mixture was concentrated under reduced pressure and subjected to flash column chromatography.

2-Diazo-4-(2,3-dihydro-1*H*-inden-1-yl)-3-oxobutanenitrile (4.6)



4.76 **4.6**

Following general procedure D, a magnetically stirred solution of β-ketonitrile **4.76** (120 mg, 0.602 mmol) in acetonitrile (5 mL) was treated with imidazolesulfonyl azide (125 mg, 0.723 mmol) and pyridine (0.24 mL, 3.01 mmol) and the resulting mixture heated at 40 °C for 22 h (CAUTION – Risk of explosion – use blast shield). The dark orange reaction mixture was then concentrated under reduced pressure and subjected to flash column chromatography (silica, 3:2 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 17:3 v/v hexane/ethyl acetate), the *title diazo-compound* ***4.6*** (106 mg, 78%) as a bright-yellow oil.

^{1}H NMR (400 MHz) δ 7.27 - 7.14 (complex m, 4H), 3.70 (m, 1H), 3.06 (dd, *J* = 16.2, 5.3 Hz, 1H), 2.94 (m, 2H), 2.79 (dd, *J* = 16.2, 8.8 Hz, 1H), 2.40 (m, 1H), 1.76 (m, 1H).

^{13}C NMR (100 MHz) δ 189.3 (CO), 144.8 (C), 143.7 (C), 127.1 (CH), 126.4 (CH), 124.7 (CH), 123.4 (CH), 108.3 (CN), 44.9 (CH_2), 40.8 (CH), 32.2 (CH_2), 31.1 (CH_2), (the signal due to the carbon bearing the diazo-group was not observed).

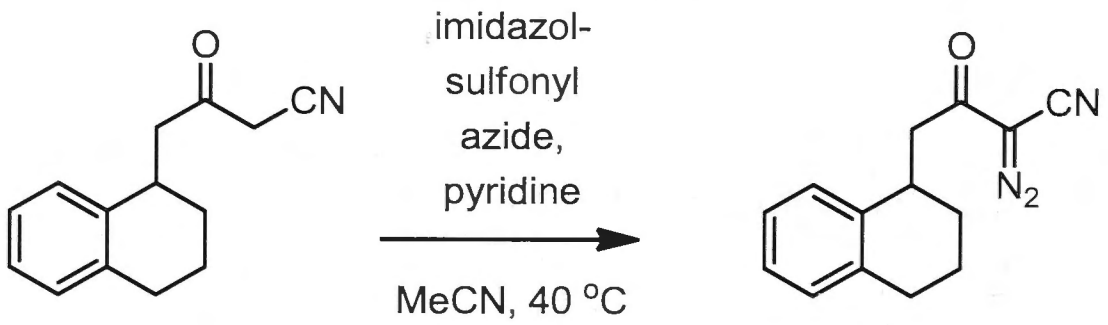
IR ν_{max} 3069, 3020, 2945, 2849, 2222, 2128, 1674 cm^{-1}.

MS (EI, 70eV) *m/z* 196 ($[M-N_2]^{+\bullet}$, 80%), 182 (15), 130 (30), 117 (100).

HREIMS found: $[M-N_2]^{+\bullet}$, 196.0771. $C_{13}H_{11}N_3O$ requires $[M-N_2]^{+\bullet}$, 196.0762.

mp 37-39 °C.

2-Diazo-3-oxo-4-(1,2,3,4-tetrahydronaphthalen-1-yl)butanenitrile (4.7)



4.77 **4.7**

Following general procedure D, a magnetically stirred solution of β-ketonitrile **4.77** (30 mg, 0.14 mmol) in acetonitrile (1.5 mL) was treated with imidazolesulfonyl azide (29 mg, 0.17 mmol) and pyridine (57 µl, 0.70 mmol) and the resulting mixture heated at 40 °C for 22 h (CAUTION – Risk of explosion – use blast shield). The dark orange reaction mixture was then concentrated under reduced pressure and subjected to flash column chromatography (silica, 3:2 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 17:3 v/v hexane/ethyl acetate), the *title diazo-compound* ***4.7*** (8 mg, 24%) as a bright-yellow oil.

^{1}H NMR (400 MHz) δ 7.12 (m, 4H), 3.49 (m, 1H), 2.94 (m, 2H), 2.78 (m, 1H), 1.91 (m, 1H), 1.81 (m, 2H), 1.73 (m, 2H).

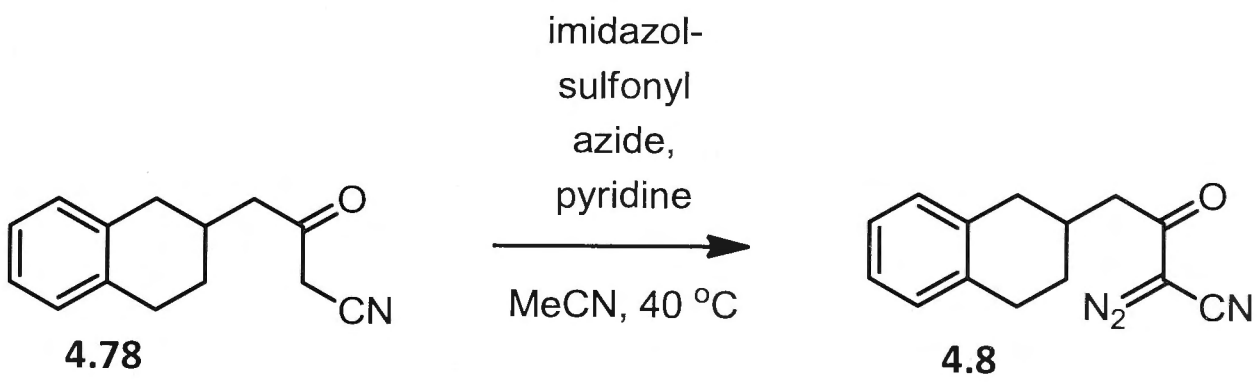
^{13}C NMR (100 MHz) δ 189.4 (CO), 138.3 (C), 137.2 (C), 129.5 (CH), 128.3 (CH), 126.4 (CH), 126.0 (CH), 108.4 (CN), 46.8 (CH_2), 34.2 (CH), 29.3 (CH_2), 27.8 (CH_2), 19.3 (CH_2), (the signal due to the carbon bearing the diazo-group was not observed).

IR ν_{max} 3060, 3017, 2929, 2221, 2129, 1673 cm^{-1}.

MS (EI, 70eV) *m/z* 239 ($M^{+\bullet}$, <1%), 211 (20%), 183 (50), 131 (100), 115 (25), 91 (30).

HREIMS found: $M^{+\bullet}$, 239.1051. $C_{14}H_{13}N_3O$ requires $M^{+\bullet}$, 239.1059.

2-Diazo-3-oxo-4-(1,2,3,4-tetrahydronaphthalen-2-yl)butanenitrile (4.8)



4.78 **4.8**

Following general procedure D, a magnetically stirred solution of β-ketonitrile **4.78** (250 mg, 1.17 mmol) in acetonitrile (12 mL) was treated with imidazolesulfonyl azide (244 mg, 1.41 mmol) and pyridine (0.47 mL, 5.9 mmol) and the resulting mixture heated at 40 °C for 22 h (CAUTION – Risk of explosion – use blast shield). The dark orange reaction mixture was then concentrated under reduced pressure and subjected to flash column chromatography (silica, 3:2 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 17:3 v/v hexane/ethyl acetate), the *title diazo-compound* ***4.8*** (218 mg, 78%) as a bright-yellow, crystalline solid.

^{1}H NMR (400 MHz) δ 7.09 (m, 4H), 2.91 (dd, *J* = 16.0, 4.4 Hz, 1H), 2.85 (m, 2H), 2.69 (d, *J* = 6.9 Hz, 2H), 2.54 (dd, *J* = 16.0, 10.7 Hz, 1H), 2.40 (m, 1H), 1.97 (m, 1H), 1.54 (m, 1H).

^{13}C NMR (100 MHz) δ 189.3 (CO), 135.9 (C), 135.1 (C), 129.1 (CH), 128.9 (CH), 125.9 (CH), 125.7 (CH), 108.4 (CN), 45.7 (CH_2), 35.5 (CH_2), 31.2 (CH), 29.1 (CH_2), 28.5 (CH_2), (the signal due to the carbon bearing the diazo-group was not observed).

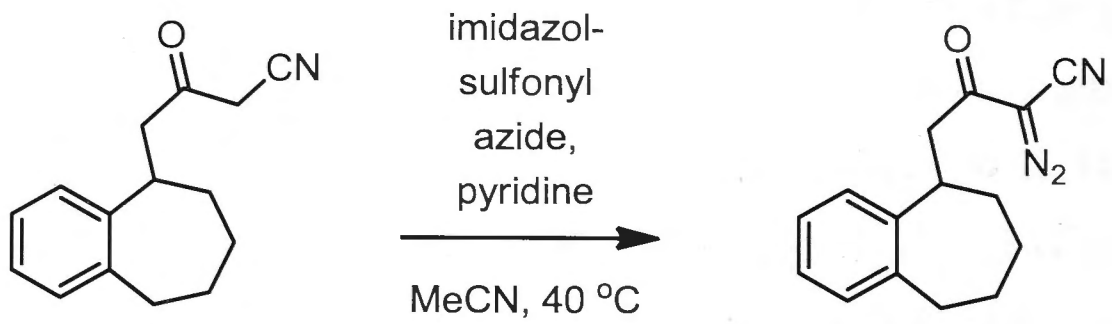
IR ν_{max} 3060, 3017, 2921, 2221, 2127, 1673 cm^{-1}.

MS (EI, 70eV) *m/z* 239 ($M^{+\bullet}$, 1%), 211 (25), 183 (20), 130 (100), 115 (35), 91 (35).

HREIMS found: $M^{+\bullet}$, 239.1060. $C_{14}H_{13}N_3O$ requires $M^{+\bullet}$, 239.1059.

mp 69-77 °C.

2-Diazo-3-oxo-4-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)butanenitrile (4.9)



4.79 **4.9**

Following general procedure D, a magnetically solution of β-ketonitrile **4.78** (132 mg, 0.581 mmol) in acetonitrile (6 mL) was treated with imidazolesulfonyl azide (120 mg, 0.697 mmol) and pyridine (234 µl, 2.90 mmol) and the resulting mixture heated at 40 °C for 22 h (CAUTION – Risk of explosion – use blast shield). The dark orange reaction mixture was then concentrated under reduced pressure and subjected to flash column chromatography (silica, 3:2 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 17:3 v/v hexane/ethyl acetate), the *title diazo-compound* ***4.9*** (131 mg, 89%) as a bright-yellow, crystalline solid.

^{1}H NMR (400 MHz) δ 7.13 (m, 3H), 7.07 (m, 1H), 3.61 (m, 1H), 3.15 (dd, *J* = 15.8, 7.1 Hz, 1H), 2.98 (dd, *J* = 15.8, 7.1 Hz, 1H), 2.88 (m, 2H), 1.84 (m, 2H), 1.75 (m, 1H), 1.71 - 1.57 (complex m, 3H).

^{13}C NMR (100 MHz) δ 189.3 (CO), 142.7 (C), 142.4 (C), 130.2 (CH), 126.7 (CH), 126.2 (2 x CH), 108.4 (CN), 44.8 (CH_2), 40.6 (CH), 36.1 (CH_2), 33.2 (CH_2), 28.5 (CH_2), 27.7 (CH_2), (the signal due to the carbon atom bearing the diazo-group was not observed).

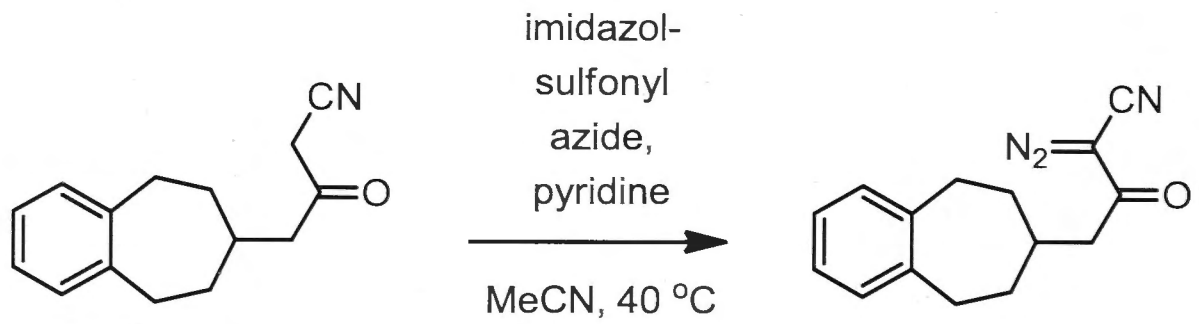
IR ν_{max} 3060, 3018, 2923, 2852, 2221, 2129, 1675 cm^{-1}.

MS (EI, 70eV) *m/z* 253 ($M^{+\bullet}$, 1%), 225 (45), 182 (40), 145 (100), 128 (35), 115 (50).

HREIMS found: $M^{+\bullet}$, 253.1212. $C_{15}H_{15}N_3O$ requires $M^{+\bullet}$, 253.1215.

mp 43-46 °C.

2-Diazo-3-oxo-4-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl)butanenitrile (4.10)



4.80 **4.10**

Following general procedure D, a magnetically stirred solution of β-ketonitrile **4.80** (325 mg, 1.43 mmol) in acetonitrile (11 mL) was treated with imidazolesulfonyl azide (300 mg,

1.72 mmol) and pyridine (0.58 mL, 7.2 mmol) and the resulting mixture heated at 40 °C for 22 h (CAUTION – Risk of explosion – use blast shield). The dark orange reaction mixture was then concentrated under reduced pressure and subjected to flash column chromatography (silica, 3:2 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 17:3 v/v hexane/ethyl acetate), the *title diazo-compound* ***4.10*** (273 mg, 75%) as a bright-yellow, crystalline solid.

^{1}H NMR (400 MHz) δ 7.13 (m, 3H), 7.07 (m, 1H), 3.61 (m, 1H), 3.15 (dd, *J* = 15.8, 7.1 Hz, 1H), 2.98 (dd, *J* = 15.8, 7.1 Hz, 1H), 2.88 (m, 2H), 1.84 (m, 2H), 1.75 (m, 1H), 1.71 - 1.57 (complex m, 3H).

^{13}C NMR (100 MHz) δ 189.5 (CO), 142.3 (C), 128.9 (CH), 126.3 (CH), 108.4 (CN), 47.1 (CH_2), 40.0 (CH), 34.5 (CH_2), 34.0 (CH_2), (the signal due to the carbon atom bearing the diazo-group was not observed).

IR ν_{max} 3063, 3020, 2917, 2847, 2222, 2131, 1674 cm^{-1}.

MS (EI, 70eV) *m/z* 253 (M^+, 1%), 225 (25), 182 (15), 143 (100), 129 (75), 117 (70), 91 (70).

HREIMS found: $[M-N_2]^{+\bullet}$, 225.1156. $C_{15}H_{15}NO$ requires $[M-N_2]^{+\bullet}$, 225.1154.

mp 98-100 °C.

The Büchner Reaction: Microwave Method - A dry microwave tube with stirrer bar was charged with a solution of diazo-β-ketonitrile in DCM under a nitrogen atmosphere. Catalyst (2 mg) was added, the tube sealed and immediately inserted into the microwave. It was heated to the specified temperature for 2 min. (2 min. ramping) and then allowed to cool to room temperature. The reaction mixture was concentrated under a stream of nitrogen and subjected to qualitative analysis using ^{1}H NMR spectroscopy.

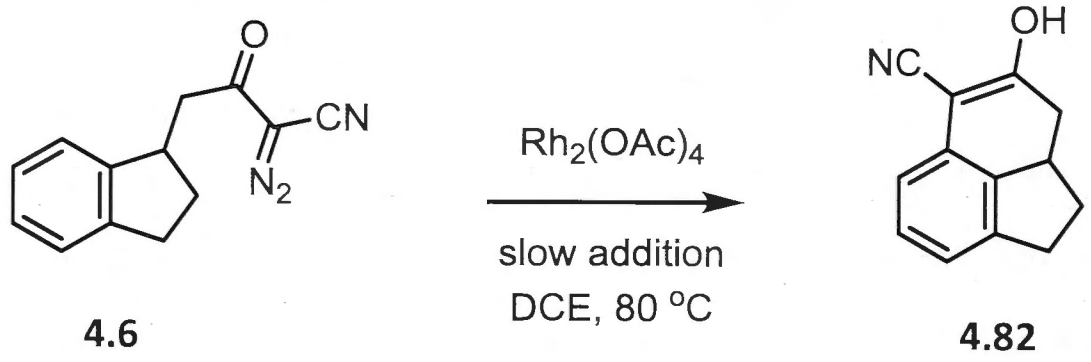
The Büchner Reaction: Slow Addition Method - A magnetically stirred dispersion of $Rh_2(OAc)_4$ (5 mol%) in DCE (10 mL) was heated at reflux (80 °C) then treated with a solution of the respective diazo-β-ketonitrile in DCM at a rate of 0.2 mmol h^{-1} (using a syringe pump). After the addition was complete, the reaction mixture was concentrated under reduced pressure and subjected to flash column chromatography.

The products formed under the various reaction conditions are given in separate tables for each starting material.

Table 1. Products Obtained from the Rhodium-Catalysed Decomposition of Diazo-β-Ketonitrile 4.6

Temperature	$Rh_2(OAc)_4$	$Rh_2(tfa)_4$
40-50 °C	**4.82**	**4.86** (91%)
80 °C	Slow addition: **4.82** (85%)	**4.86**
120 °C	**4.82**	**4.86**, **4.82** (2:1 ratio by NMR)

4-Hydroxy-1,2,2a,3-tetrahydroacenaphthylene-5-carbonitrile (4.82)



4.6 **4.82**

Using the slow addition method, diazo-β-ketonitrile **4.6** (50 mg, 0.22 mmol) was subjected to reaction with $Rh_2(OAc)_4$ at 80 °C. Subjection of the resulting pale-yellow crude solid to flash column chromatography (silica, 1:1 PS 30-40/diethyl ether elution) yielded, after concentration of the appropriate fractions (R_f = 0.2 in 13:7 v/v hexane/ethyl acetate), the *title enol* ***4.82*** (37 mg, 85%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz) δ 7.18 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 3.36 (m, 1H), 2.95 (dd, *J* = 10.0, 3.4 Hz, 1H), 2.75 (dd, *J* = 16.9, 7.4 Hz, 1H), 2.50 (m, 1H), 2.48 (d, *J* = 15.5 Hz, 1H), 2.35 (covered, 1H), 1.75 (m, 1H).

^{13}C NMR (100 MHz) δ 171.1 (C), 141.5 (CH), 137.4 (C), 128.1 (CH), 126.6 (C), 122.7 (CH), 199.5 (CH), 115.7 (C), 110.0 (CH), 85.4 (C), 44.1 (C), 38.5 (CH), 35.5 (CH_2), 34.5 (CH_2), 32.6 (CH_2).

IR ν_{max} 3152, 2958, 2860, 2213, 1624, 1597 cm^{-1}.

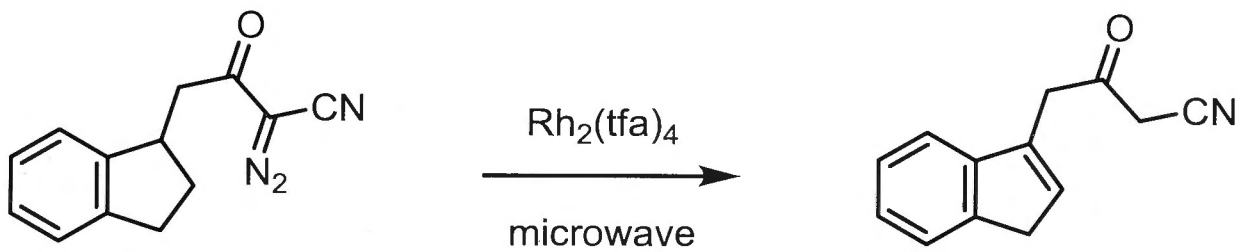
MS (EI, 70eV) *m/z* 197 (M^+, 100%), 182 (35), 155 (70), 128 (20), 115 (30).

HREIMS found: $M^{+\bullet}$, 197.0844. $C_{13}H_{11}NO$ requires $M^{+\bullet}$, 197.0841.

mp 195-199 °C.

X-ray (see Appendix 7).

4-(1*H*-Inden-3-yl)-3-oxobutanenitrile (4.86)



4.6 **4.86**

Using the microwave method, diazo-β-ketonitrile **4.6** (5 mg, 0.02 mmol) was subjected to reaction with $Rh_2(tfa)_4$ at 40 °C. Flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) of the crude material gave, after concentration of the appropriate fractions (R_f = 0.4 in 13:7 v/v hexane/ethyl acetate), the *title β-ketonitrile* ***4.86*** (4 mg, 91%) as a yellow oil, which darkened within hours while stored at 4 °C.

^{1}H NMR (400 MHz) δ 7.50 (d, *J* = 7.3 Hz, 1H), 7.30 (m, 3H), 6.53 (s, 1H), 3.84 (s, 2H), 3.52 (s, 2H), 3.45 (s, 2H).

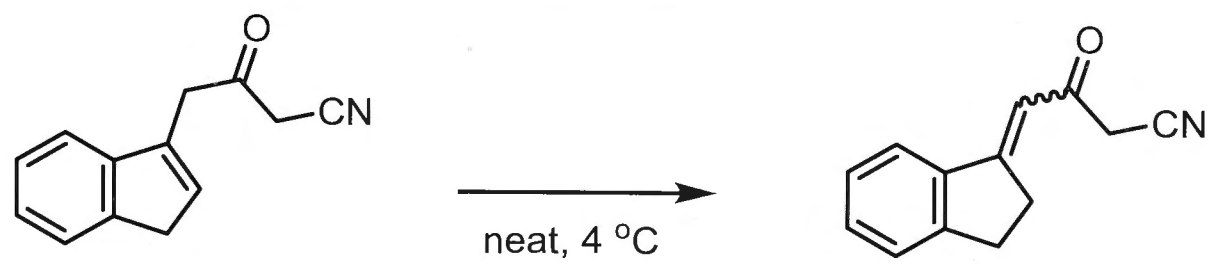
^{13}C NMR (100 MHz) δ 171.1 (C), 141.5 (CH), 137.4 (C), 128.1 (CH), 126.6 (C), 122.7 (CH), 199.5 (CH), 115.7 (C), 110.0 (CH), 85.4 (C), 44.1 (C), 38.5 (CH), 35.5 (CH_2), 34.5 (CH_2), 32.6 (CH_2).

IR ν_{max} 3020, 2916, 2847, 2257, 2202, 1730 cm^{-1}.

MS (EI, 70eV) *m/z* 197 ($M^{+\bullet}$, 50%), 155 (55), 129 (35), 115 (100).

HREIMS found: $M^{+\bullet}$, 197.0838. $C_{13}H_{11}NO$ requires $M^{+\bullet}$, 197.0841.

4-(2,3-Dihydro-1*H*-inden-1-ylidene)-3-oxobutanenitrile (4.87)



4.86 **4.87**

A sample of 4-(1*H*-inden-3-yl)-3-oxobutanenitrile **4.86** was stored at 4 °C over several months and cleanly isomerised to give the *title β-ketonitrile* ***4.87*** as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.43 (m, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.86 (m, 1H), 3.58 (s, 2H), 3.34 (m, 2H), 3.14 (t, *J* = 5.6 Hz, 2H).

^{13}C NMR (100 MHz) δ 185.8 (CO), 151.5 (C), 139.2 (C), 132.4 (CH), 127.1 (CH), 125.9 (CH), 125.2 (C), 122.2 (CH), 114.8 (CN), 110.9 (CH), 32.9 (CH_2), 32.7 (CH_2), 30.8 (CH_2).

IR ν_{max} 3020, 2918, 2345, 2260, 1683, 1591 cm^{-1}.

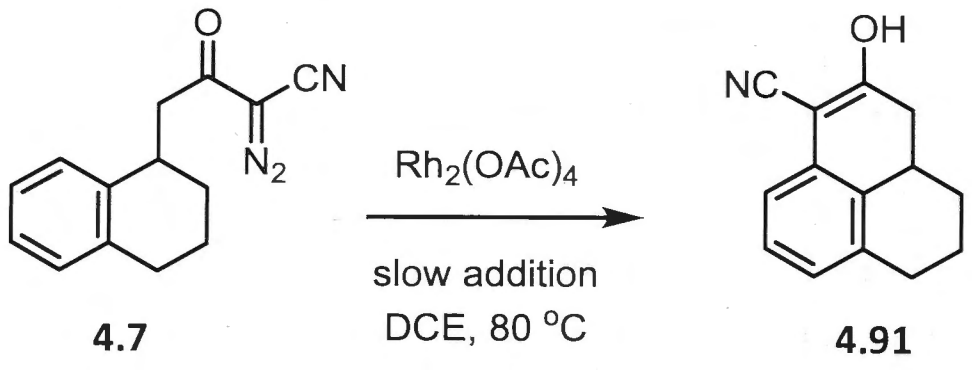
MS (EI, 70eV) *m/z* 197 ($M^{+\bullet}$, 20%), 157 (100), 128 (35).

HREIMS found: $M^{+\bullet}$, 197.0844. $C_{13}H_{11}NO$ requires $M^{+\bullet}$, 197.0841.

Table 2. Products Obtained from the Rhodium-Catalysed Decomposition of Diazo-β-Ketonitrile 4.7

Temperature	$Rh_2(OAc)_4$	$Rh_2(tfa)_4$
40-50 °C	**4.91**	**4.91**, **4.92** (1:1 ratio by NMR)
80 °C	Slow addition: **4.91** (22%)	**4.91**, **4.92** (1:1 ratio by NMR)
120 °C	decomposition	**4.91**, **4.92** (2:1 ratio by NMR)

2-Hydroxy-7,8,9,9a-tetrahydro-1*H*-phenalene-3-carbonitrile (4.91)



4.7 **4.91**

Using the microwave method, diazo-β-ketonitrile **4.7** (10 mg, 0.042 mmol) was subjected to reaction with $Rh_2(OAc)_4$ (2 mg) at 40 °C. Flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) of the crude pale-yellow oil gave, after concentration of the appropriate fractions (R_f = 0.5 in 13:7 v/v hexane/ethyl acetate), the *title enol* ***4.91*** (2 mg, 22%) as an off-white wax.

Due to decomposition during the purification process the above structure was assigned by the characteristic signals in the ^{1}H NMR spectrum of the crude material. These characteristic resonances were analogous to those observed for compound **4.82**.

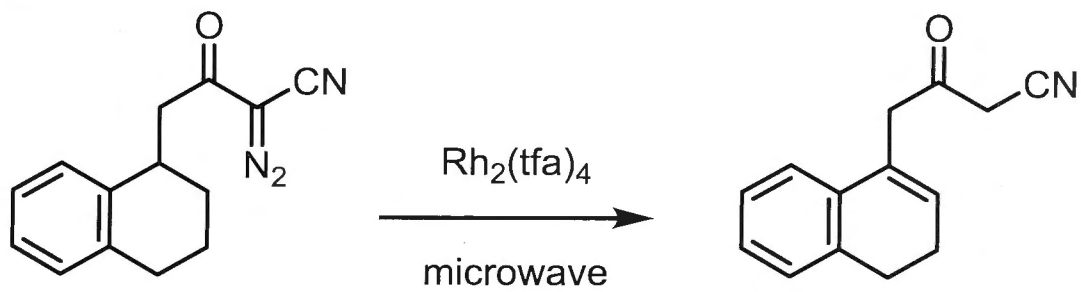
Compound 4.91

^{1}H NMR (400 MHz) δ 7.49 (m, 1H), 7.24 (m, 2H), 7.17 (m, 1H), 3.73 (dd, *J* = 11.8, 6.1 Hz, 1H), 3.25 (d, *J* = 11.8 Hz, 1H), 2.89 (m, 2H), 2.81 (dd, *J* = 19.0, 8.3 Hz, 1H), 2.76 - 2.67 (complex m, 1H), 2.42 (d, *J* = 19.0 Hz, 1H), 1.95 (m, 1H), 1.56 - 1.44 (complex m, 1H).

MS (EI, 70eV) *m/z* 211 ($M^{+\bullet}$, 30%), 195 (100), 168 (45).

HREIMS found: $M^{+\bullet}$, 211.0995. $C_{13}H_{11}NO$ requires $M^{+\bullet}$, 211.0997.

4-(3,4-Dihydronaphthalen-1-yl)-3-oxobutanenitrile (4.92)



4.7 **4.92**

Using the microwave method, diazo-β-ketonitrile **4.7** (15 mg, 0.063 mmol) was subjected to reaction with $Rh_2(tfa)_4$ at 80 °C. According to the ^{1}H NMR spectrum of the crude product, compounds **4.91** and **4.92** were present as a mixture as specified in the above table. Subjection to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) yielded, after concentration of the appropriate fractions (R_f = 0.5 in 13:7 v/v hexane/ethyl acetate), the *title β-ketonitrile* ***4.92*** (<1 mg) as a clear, colourless oil.

Due to decomposition during the purification process the above structure was assigned by the characteristic signals in the ^{1}H NMR spectrum of the crude material. These characteristic resonances were analogous to those observed for compound **4.86**.

Compound 4.92

^{1}H NMR (400 MHz) δ 7.49 (m, 1H), 7.24 (m, 2H), 7.17 (m, 1H), 3.73 (dd, *J* = 6.1, 11.8 Hz, 1H), 3.25 (d, *J* = 11.8 Hz, 1H), 2.89 (m, 2H), 2.81 (dd, *J* = 8.3, 19.0 Hz, 1H), 2.76-2.67 (complex m, 1H), 2.42 (d, *J* = 19.0 Hz, 1H), 1.95 (dq, *J* = 3.9, 13.6 Hz, 1H), 1.56-1.44 (complex m, 1H).

MS (EI, 70eV) *m/z* 211 ($M^{+\bullet}$, 10%), 171 (55), 129 (100).

HREIMS found: $M^{+\bullet}$, 211.0996. $C_{13}H_{11}NO$ requires $M^{+\bullet}$, 211.0997.

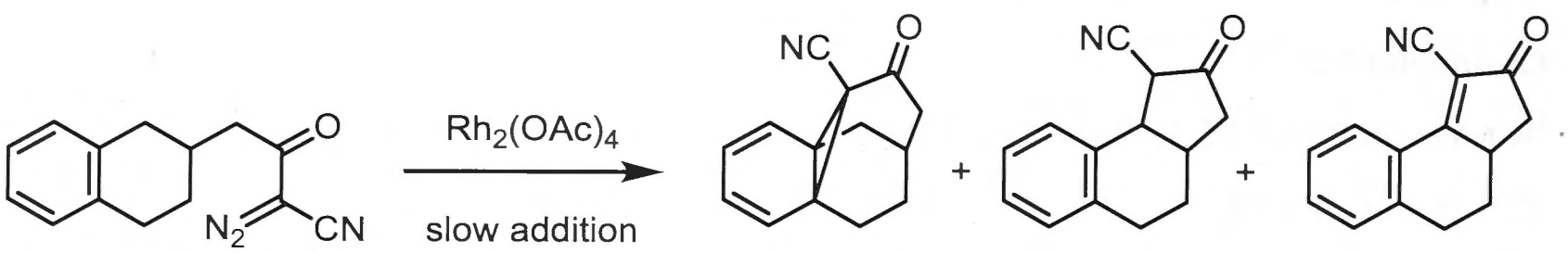
Table 3. Products Obtained from the Rhodium-Catalysed Decomposition of Diazo-β-Ketonitrile 4.8

Temperature	$Rh_2(OAc)_4$	$Rh_2(tfa)_4$
40-50 °C	**4.96**	**4.96**, **4.94** (2:1 ratio by NMR)
80 °C	Slow addition: **4.94** (50%), **4.93**/**4.95** (1:1 ratio, 9%)	**4.96**, **4.94** (1:1 ratio by NMR)
120 °C	**4.94**, **4.96** (trace: **4.93**)	**4.96**, **4.94** (1:1 ratio by NMR)

5-Oxo-4b,5,6,7,8,9-hexahydro-4a,7-methanobenzo[1,3]cyclopropa[1,2][7]annulene-4b-carbonitrile (4.93),

2-Oxo-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-1-carbonitrile (4.94) and

2-Oxo-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*a*]naphthalene-1-carbonitrile (4.95)



4.8 DCE, 80 °C **4.93** **4.94** **4.95**

Using the slow addition method, diazo-β-ketonitrile **4.8** (50 mg, 0.21 mmol) was subjected to reaction with $Rh_2(OAc)_4$ (5 mg) at 80 °C. The resulting crude product was subjected to flash column chromatography (silica, 13:7 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions, three compounds, A, B and C.

Concentration of fraction **A** (R_f = 0.5 in 13:7 v/v hexane/ethyl acetate) gave the *title β-ketonitrile* ***4.94*** (22 mg, 50%) as an off-white wax.

Compound 4.94

^{1}H NMR (400 MHz) δ 7.49 (m, 1H), 7.24 (m, 2H), 7.17 (m, 1H), 3.73 (dd, *J* = 11.3, 6.1 Hz, 1H), 3.25 (d, *J* = 11.3 Hz, 1H), 2.89 (m, 2H), 2.81 (dd, *J* = 19.0, 8.3 Hz, 1H), 2.76 - 2.67 (complex m, 1H), 2.42 (d, *J* = 19.0 Hz, 1H), 1.95 (dq, *J* = 13.6, 3.9 Hz, 1H), 1.56 - 1.44 (complex m, 1H).

^{13}C NMR (100 MHz) δ 205.7 (CO), 135.2 (C), 133.8 (C), 129.5 (CH), 129.3 (CH), 127.7 (CH), 126.8 (CH), 116.7 (CN), 45.6 (CH), 44.7 (CH_2), 43.4 (CH), 33.3 (CH), 28.7 (CH_2), 25.7 (CH_2).

IR ν_{max} 2922, 2852, 2244, 1755, 1667 cm^{-1}.

MS (EI, 70eV) *m/z* 211 ($M^{+\bullet}$, 90%), 210 (100), 167 (35), 129 (95), 115 (35).

HREIMS found: $M^{+\bullet}$, 211.0996. $C_{14}H_{13}NO$ requires $M^{+\bullet}$, 211.0997.

mp 64-67 °C.

Concentration of fraction **B** (R_f = 0.4 in 13:7 v/v hexane/ethyl acetate) gave the *title compounds **4.93** and **4.95*** as a 1:1 mixture (4 mg, 9%). While a small amount of pure and crystalline compound **4.95** could be obtained, the spectral data for propellane **4.93** was obtained by subtracting the signals of the NMR spectra from those of compound **4.95**.

Compound 4.95

^{1}H NMR (400 MHz) δ 8.45 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 3.21 (m, 1H), 3.10 (m, 2H), 2.92 (dd, *J* = 18.7, 6.8, 1H), 2.39 (m, 1H), 2.35 (m, 1H), 2.30 (dd, *J* = 18.8, 4.0, 1H), 1.79 (m, 1H), 1.25 (m, 1H).

^{13}C NMR (100 MHz) δ 200.7 (CO), 181.0 (C), 141.3 (C), 133.9 (CH), 129.9 (CH), 128.8 (CH), 128.7 (CH), 128.1 (C), 127.3 (CH), 108.7 (CN), 41.3 (CH_2), 40.3 (CH), 29.8 (CH_2), 29.8 (CH_2).

IR ν_{max} 2921, 2850, 2237, 2213, 1785, 1756 1653 cm^{-1}.

MS (EI, 70eV) *m/z* 209 ($M^{+\bullet}$, 100%), 181 (55), 153 (40), 128 (20), 117 (15).

HREIMS found: $M^{+\bullet}$, 209.0843. $C_{14}H_{11}NO$ requires $M^{+\bullet}$, 209.0841.

mp 125-130 °C.

X-ray (see Appendix 8).

Compound 4.93

^{1}H NMR (400 MHz) δ 6.38 (dd, *J* = 9.3, 6.3 Hz, 1H), 6.31 (dd, *J* = 8.3, 5.3 Hz, 1H), 6.07 (d, *J* = 9.2 Hz, 1H), 5.94 (d, *J* = 9.2 Hz, 1H), (dd, *J* = 19.6, 5.8 Hz, 1H), 2.49 (m, 2H), 2.47 - 2.37 (covered, 3H), 2.13 (dd, *J* = 16.5, 7.6 Hz, 1H), 2.10 (m, 1H), 1.69 (m, 1H).

^{13}C NMR (100 MHz) δ 201.6 (CO), 129.2 (CH), 127.6 (CH), 126.1 (CH), 125.2 (CH), 41.6 (CH_2), 30.9 (CH), 30.6 (C), 26.7 (CH_2), 26.7 (CH_2), 25.9 (CH_2), (the signals due to two quaternary carbon atoms obscured).

IR ν_{max} 2931, 2867, 2238, 1713, 1684, 1590 cm^{-1}.

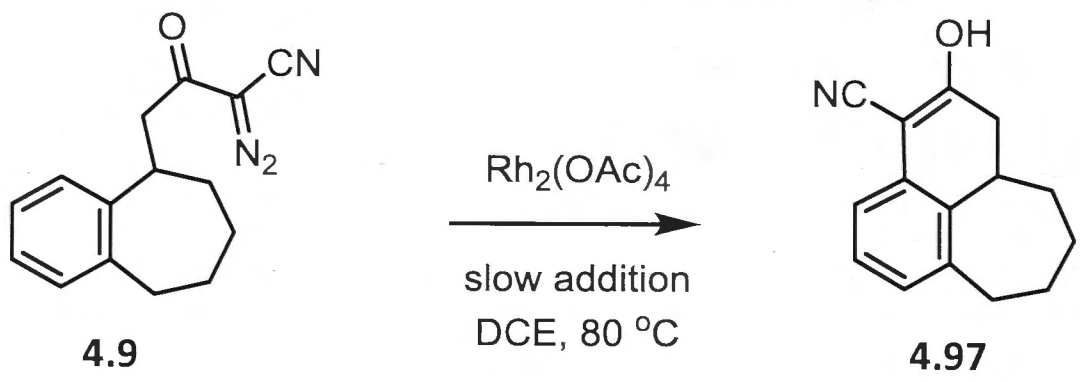
MS (EI, 70eV) *m/z* 211 ($M^{+\bullet}$, 30%), 168 (70), 154 (100), 129 (95), 117 (45).

HREIMS found: $M^{+\bullet}$, 211.0996. $C_{14}H_{13}NO$ requires $M^{+\bullet}$, 211.0997.

Table 4. Products Obtained from the Rhodium-Catalysed Decomposition of Diazo-β-Ketonitrile 4.9

Temperature	$Rh_2(OAc)_4$	$Rh_2(tfa)_4$
40-50 °C	**4.97**	**4.97**, **4.98** (1:1 ratio by NMR)
80 °C	Slow addition: **4.97** (54%)	**4.97** (55%), **4.98** (24%) (1:1 ratio by NMR)
120 °C	**4.97**	**4.97**, **4.98** (1:1 ratio by NMR)

2-Hydroxy-1,7,8,9,10,10a-hexahydrocyclohepta[*de*]naphthalene-3-carbonitrile (4.97)



4.9 **4.97**

Using the slow addition method, diazo-β-ketonitrile **4.9** (50 mg, 0.20 mmol) was subjected to reaction with $Rh_2(OAc)_4$ (4 mg) at 80 °C. The resulting crude yellow oil was subjected to flash column chromatography (silica, 7:3 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 13:7 v/v hexane/ethyl acetate), the *title β-ketonitrile* ***4.97*** (24 mg, 72%) as a pale-yellow, crystalline solid.

^{1}H NMR (400 MHz) δ 7.18 - 7.10 (complex m, 2H), 6.95 (dd, *J* = 7.0, 1.4 Hz, 1H), 3.31 (m, 1H), 3.04 - 2.94 (covered, 1H), 2.96 (m, 1H), 2.70 (dq, *J* = 14.1, 2.8 Hz, 1H), 2.39 (dd, *J* = 17.8, 2.1 Hz, 1H), 1.93 - 1.83 (complex m, 1H), 1.82 - 1.64 (complex m, 2H), 1.64 - 1.56 (complex m, 2H), 1.34 - 1.22 (complex m, 1H).

^{13}C NMR (100 MHz) δ 168.2 (C), 142.0 (C), 133.8 (C), 127.6 (C), 127.2 (CH), 126.9 (CH), 121.8 (CH), 116.3 (CN), 84.8 (C), 35.6 (CH_2), 35.2 (CH), 34.5 (CH_2), 34.0 (CH_2), 29.7 (CH_2), 26.5 (CH_2).

IR ν_{max} 3169, 3036, 2924, 2852, 2217, 1649, 1622 cm^{-1}.

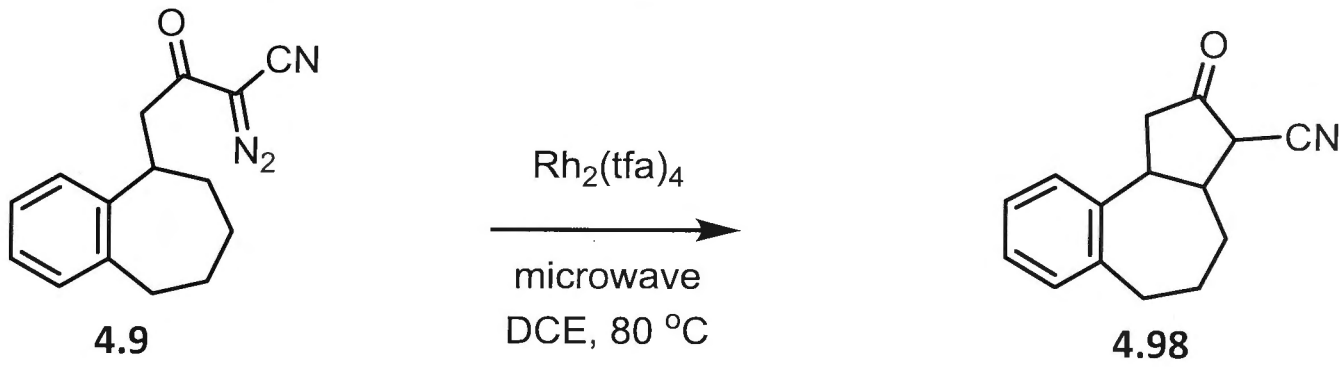
MS (EI, 70eV) *m/z* 225 ($M^{+\bullet}$, 100%), 183 (70), 141 (20), 128 (15), 115 (15).

HREIMS found: $M^{+\bullet}$, 225.1154. $C_{15}H_{15}NO$ requires $M^{+\bullet}$, 225.1154.

mp 167-173 °C.

X-ray (see Appendix 9).

2-Oxo-1,2,3,3a,4,5,6,10b-octahydrobenzo[*e*]azulene-3-carbonitrile (4.98)



4.9 **4.98**

Using the microwave method, diazo-β-ketonitrile **4.9** (40 mg, 0.16 mmol) was subjected to reaction with $Rh_2(tfa)_4$ (2 mg) at 80 °C. According to the ^1H NMR spectrum of the crude product, compounds **4.97** and **4.98** were present as a 1:1 mixture. Subjection of the crude yellow oil to flash column chromatography (silica, 6:4 v/v PS 30-40/diethyl ether elution) yielded two fractions, A and B.

Concentration of fraction **A** (R_f = 0.5 in 13:7 v/v hexane/ethyl acetate) gave the *title β-ketonitrile* ***4.98*** (9 mg, 24%) as an off-white wax.

Compound 4.98

^{1}H NMR (400 MHz) δ 7.25 - 7.17 (complex m, 3H), 7.12 (m, 1H), 3.44 (m, 1H), 3.09 (d, *J* = 11.9 Hz, 1H), 3.00 (d, *J* = 12.4 Hz, 1H), 2.90 (m, 2H), 2.85 (covered, 1H), 2.60 (m, 1H), 2.24 (dq, *J* = 11.2, 3.5 Hz, 1H), 2.17 - 2.09 (complex m, 1H), 1.69 (dq, *J* = 11.7, 3.4 Hz, 1H), 1.55 - 1.43 (complex m, 1H).

^{13}C NMR (100 MHz) δ 203.8 (CO), 143.3 (C), 138.2 (C), 130.1 (CH), 127.5 (CH), 126.6 (CH), 124.9 (CH), 115.7 (CN), 48.5 (CH), 46.9 (CH), 43.6 (CH), 42.5 (CH_2), 37.8 (CH_2), 36.6 (CH_2), 26.5 (CH_2).

IR ν_{max} 2925, 2854, 2246, 1755, 1656 cm^{-1}.

MS (EI, 70eV) *m/z* 225 ($M^{+\bullet}$, 100%), 183 (50), 143 (55), 129 (30), 115 (45), 91 (25).

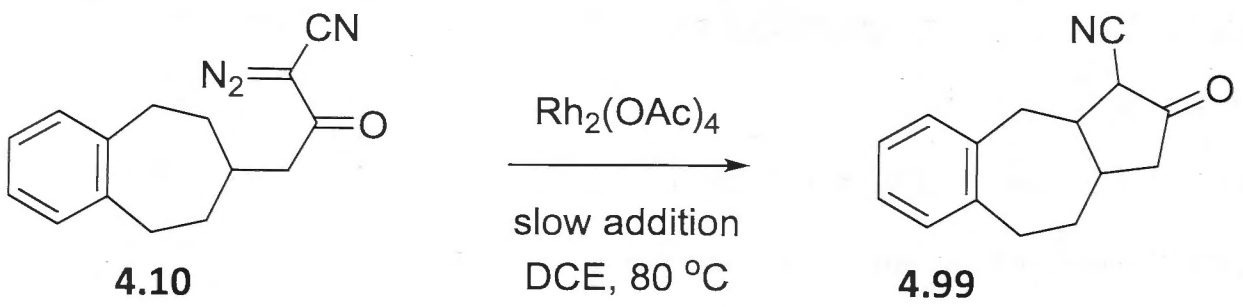
HREIMS found: $M^{+\bullet}$, 225.1152. $C_{15}H_{15}NO$ requires $M^{+\bullet}$, 225.1154.

Concentration of fraction **B** (R_f = 0.2 in 13:7 v/v hexane/ethyl acetate) gave the *title β-ketonitrile* ***4.97*** (17 mg, 55%) as a pale-yellow, crystalline solid. This material was identical, in all respects, with an authentic sample.

Table 5. Products Obtained from the Rhodium-Catalysed Decomposition of Diazo-β-Ketonitrile 4.10

Temperature	$Rh_2(OAc)_4$	$Rh_2(tfa)_4$
40-50 °C	**4.99**	**4.99**
80 °C	Slow addition: **4.99** (70%)	**4.99**
120 °C	**4.99**	**4.99**

2-Oxo-1,2,3,3a,4,9,10,10a-octahydrobenzo[f]azulene-3-carbonitrile (4.99)



4.10 **4.99**

Using the slow addition method, diazo-β-ketonitrile **4.10** (50 mg, 0.20 mmol) was subjected to reaction with $Rh_2(OAc)_4$ (4 mg) at 80 °C. The resulting crude yellow oil was subjected to flash column chromatography (silica, 65:35 v/v PS 30-40/diethyl ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 65:35 v/v hexane/ethyl acetate), the *title β-ketonitrile* ***4.99*** (31 mg, 70%) as a pale-yellow wax.

^{1}H NMR (400 MHz) δ 7.24 - 7.14 (complex m, 4H), 3.10 (d, *J* = 17.5 Hz, 1H), 3.10 (d, *J* = 9.4 Hz, 1H), 3.02 (d, *J* = 10.1 Hz, 1H), 2.89 (m, 2H), 2.65 (m, 1H), 2.23 (m, 1H), 2.08 (m, 1H), 2.14 - 1.95 (complex m, 2H), 1.36 (m, 1H).

^{13}C NMR (100 MHz) δ 203.7 (CO), 141.5 (C), 138.8 (C), 130.0 (CH), 129.8 (CH), 127.2 (CH), 126.8 (CH), 115.7 (CN), 47.9 (CH), 47.3 (CH), 46.9 (CH), 45.0 (CH_2), 38.7 (CH_2), 35.2 (CH_2), 31.8 (CH_2).

IR ν_{max} 3017, 2919, 2853, 2246, 1756 cm^{-1}.

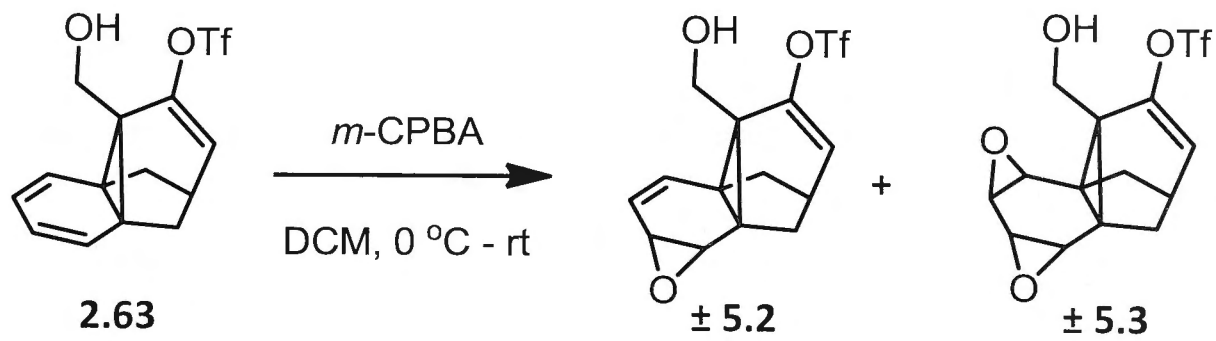
MS (EI, 70eV) *m/z* 225 ($M^{+\bullet}$, 100%), 182 (20), 143 (30), 129 (50), 115 (40), 104 (50), 91 (30).

HREIMS found: $M^{+\bullet}$, 225.1152. $C_{14}H_{11}NO$ requires $M^{+\bullet}$, 225.1154.

6.5. Experimental Procedures for Chapter 5

(1a*SR*,1b*SR*,3*RS*,5a*SR*,5b*RS*,7a*RS*)-5a-(Hydroxymethyl)-2,3,5a,7a-tetrahydro-1a*H*-3,5b-methanobenzo[1',3']cyclopropa[1',2':3,4]benzo[1,2-*b*]oxiren-5-yl trifluoromethanesulfonate (± 5.2) and

(1a*SR*,1b*SR*,2a*SR*,2b*RS*,2c*SR*,5*RS*,6a*SR*,6b*SR*)-2c-(Hydroxymethyl)-1b,2a,2c,5,6,6b-hexahydro-1a*H*-2b,5-methanobenzo[1',3']cyclopropa[1',2':5,6]benzo[1,2-b:3,4-*b*']bis(oxirene)-3-yl trifluoromethanesulfonate (± 5.3)



2.63 **± 5.2** **± 5.3**

Achiral Method - A magnetically stirred solution of alcohol **2.63** (60 mg, 0.18 mmol) in DCM (4 mL) maintained at 0 °C was treated with *m*-CPBA (>77 %, 40 mg, 0.18 mmol) and stirring continued at room temperature for 21 h. The reaction was then quenched with $NaHCO_3$ (5 mL of a sat. aq. solution) and the separated aqueous layer extracted with DCM (1 x 5 mL), the combined organic layers dried ($MgSO_4$), filtered, and concentrated under reduce pressure. Subjection of the resulting pale-yellow oil to flash column chromatography (silica, 1:1 – 3:7 v/v PS 30-40/diethyl ether gradient elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.6 in 2:3 hexane/ethyl acetate) gave the *title bisepoxide* ***± 5.3*** (4 mg, 6%) as a clear, colourless oil.

Compound ± 5.3

^{1}H NMR (400 MHz) δ 5.85 (d, *J* = 7.9 Hz, 1H), 4.77 (d, *J* = 3.0 Hz, 1H), 4.39 (s, 1H), 4.37 (d, *J* = 10.5 Hz, 1H), 3.85 (d, *J* = 10.4 Hz, 1H), 3.39 (m, 2H), 2.80 (m, 1H), 1.90 (dt, *J* = 11.4, 4.6 Hz, 2H), 1.18 (d, *J* = 12.0 Hz, 2H).

^{13}C NMR (100 MHz) δ 143.1 (C), 115.0 (CH), 73.6 (CH), 64.5 (CH_2), 63.8 (CH), 54.2 (CH), 53.3 (CH), 40.7 (C), 39.5 (C), 33.8 (C), 31.9 (CH_2), 31.4 (CH), 28.1 (CH_2), (the signals due to the CF_3-group were not observed).

IR ν_{max} 3430, 2932, 1721, 1647, 1420, 1213 cm^{-1}.

MS (EI, 70eV) *m/z* 366 ($M^{+\bullet}$, 10%), 350 (20), 267 (100), 133 (80), 115 (65), 91 (75).

HREIMS found: $M^{+\bullet}$, 366.0407. $C_{14}H_{13}O_6F_3S$ requires $M^{+\bullet}$, 366.0385.

Concentration of fraction **B** (R_f = 0.4 in 2:3 hexane/ethyl acetate) gave the *title epoxide* ***± 5.2*** (20 mg, 32%) as a clear, colourless oil.

Compound ± 5.2

^{1}H NMR (400 MHz) δ 6.59 (d, *J* = 9.4 Hz, 1H), 5.98 (d, *J* = 8.2 Hz, 1H), 5.90 (dd, *J* = 9.3, 6.2 Hz, 1H), 4.32 (d, *J* = 4.2 Hz, 1H), 4.28 (d, *J* = 11.9 Hz, 1H), 4.22 (d, *J* = 4.0 Hz, 1H), 3.73 (d, *J* = 11.8 Hz, 1H), 2.85 (m, 1H), 2.09 (dd, *J* = 12.0, 4.7 Hz, 1H), 1.85 (dd, *J* = 12.0, 4.7 Hz, 1H), 1.21 (d, *J* = 11.7 Hz, 2H).

^{13}C NMR (100 MHz) δ 143.0 (C), 133.8 (CH), 119.9 (CH), 118.7 (q, *J* = 310 Hz, CF_3), 117.0 (CH), 69.4 (CH), 61.8 (CH), 57.4 (CH_2), 39.3 (C), 38.7 (CH_2), 34.7 (C), 33.5 (CH), 31.3 (C), 27.6 (CH_2).

IR ν_{max} 3429, 2933, 1721, 1647, 1420, 1214 cm^{-1}.

MS (EI, 70eV) *m/z* 350 ($M^{+\bullet}$, 65%), 199 (45), 132 (100), 115 (40), 91 (40).

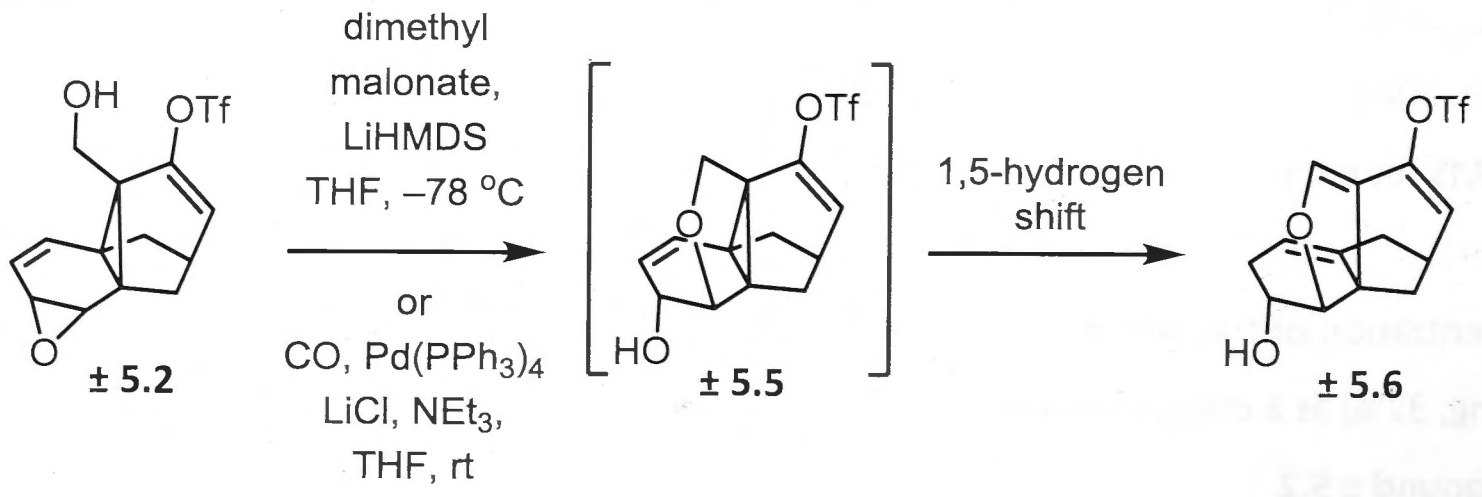
HREIMS found: $M^{+\bullet}$, 350.0438. $C_{14}H_{13}F_3O_5S$ requires $M^{+\bullet}$, 350.0436.

Shi Epoxidation Method - A magnetically stirred solution of alcohol **2.63** (8 mg, 0.02 mmol) in 2,2-dimethoxypropane (0.5 mL) was treated with Shi's ketone (2 mg, 5 µmol), buffer (0.25 mL, pH = 9, 0.1 M, K_2CO_3-AcOH in EDTA) and Bu_4NHSO_4 (1 mg, 0.0.96 µmol), and cooled to −10 °C. A solution of oxone (6 mg, 0.04 mmol) in EDTA (0.2 mL) and a solution of K_2CO_3 (20 mg, 0.14 mmol) in EDTA (0.2 mL) were then added separately but at the same time over 0.5 h. The reaction mixture was stirred at room temperature for 48 h, then diluted with hexane (5 mL), extracted with diethyl ether (2 x 5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting yellow oil to flash column chromatography (7:3 – 3:7 v/v PS 30-40/diethyl ether gradient elution) gave two fractions, A and B.

Concentration of fraction **A** (R_f = 0.8 in 2:3 hexane/ethyl acetate) yielded compound **2.63** (2 mg, 25%) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.1 in 2:3 hexane/ethyl acetate) gave the *title mono-epoxide* ***± 5.2*** (1 mg, 12%) as a colourless oil. This material was identical, in all respects, with an authentic sample.

(2a1*SR*,3*RS*,7*RS*)-3-Hydroxy-2a,3,6,7-tetrahydro-4*H*-2a1,7-methanocyclohepta-[cd]benzofuran-9-yl trifluoromethanesulfonate, (Oxa-[5.6.5.6]fenestratrienol, ± 5.6)



Method 1: Addition of a Nucleophile - A magnetically stirred mixture of dimethyl malonate (2 µl, 0.02 mmol) and LiHMDS (1 M solution in THF, 17 µl, 0.017 mmol) was treated with a solution of epoxide **± 5.2** (5 mg, 0.01 mmol) in THF (0.25 mL) at −78 °C then allowed to slowly warm to room temperature and stirring continued for 20 h. HCl (0.5 mL of a 0.5 M aq. solution) was added and the mixture extracted with diethyl ether (3 x 1 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting yellow oil to flash column chromatography (1:1 v/v PS 30-40/diethyl ether) gave, after concentration of the appropriate fractions (R_f = 0.6 in 2:3 v/v hexane/ethyl acetate), the *title fenestrane* ***± 5.6*** (1 mg, 99% brsm.) as a colourless oil.

Method 2*: *Carbonylative Coupling - Epoxide **± 5.2** (8 mg, 0.02 mmol) was subjected to standard carbonylative coupling conditions (see Experimental section for Chapter 2) to give, after concentration of the appropriate fractions (R_f = 0.6 in 2:3 v/v hexane/ethyl acetate), the *title fenestrane* ***± 5.6*** (1 mg, 50% brsm.) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 6.47 (s, 1H), 5.87 (d, *J* = 7.6 Hz, 1H), 5.66 (s, 1H), 4.63 (dd, *J* = 5.5, 4.0 Hz, 1H), 4.29 (s, 1H), 2.87 (m, 1H), 2.68 (m, 1H), 2.59 (m, 1H), 2.31 (dq, *J* = 19.9, 3.1 Hz, 1H), 1.98 (dd, *J* = 11.0, 4.2 Hz, 1H), 1.77 (d, *J* = 10.9 Hz, 1H).

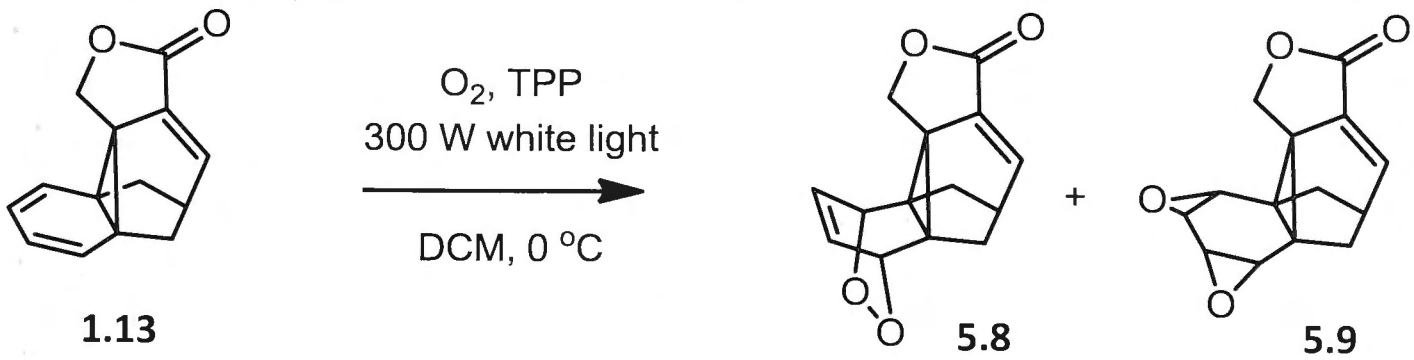
^{13}C NMR (125 MHz) δ 144.2 (C), 143.0 (C), 136.5 (CH), 120.3 (CH), 117.3 (CH), 116.4 (C), 72.6 (CH), 65.9 (CH), 46.3 (C), 39.3 (CH_2), 34.8 (CH_2), 33.1 (CH), 31.3 (CH_2).

IR ν_{max} 3442, 2958, 1723, 1648, 1608 cm^{-1}.

MS (EI, 70eV) *m/z* 350 ($M^{+\bullet}$, 100%), 217 (25), 128 (25), 115 (10).

HREIMS found: $M^{+\bullet}$, 350.0438. $C_{14}H_{13}F_3O_5S$ requires $M^{+\bullet}$, 350.0436.

(5*r*,6a*R*,7*R*,10*S*,10a*S*,10b*r*)-5,6,7,10-Tetrahydro-7,10-epidioxy-5,10a-methanobenzo-[1,3]cyclopropa[1,2-*h*]isobenzofuran-3(1*H*)-one (5.8) and (1a*S*,1b*R*,2a*R*,2b*S*,2c*r*,7*r*,8a*R*,8b*S*)-1b,2a,3,7,8,8b-Hexahydro-2b,7-methanobis(oxireno)-[2'',3'':3',4';2''',3''':5',6']benzo[1',2':2,3]cyclopropa[1,2-*d*]isobenzofuran-5(1a*H*)-one (5.9)



1.13 **5.8** **5.9**

A magnetically stirred solution of *meso*-compound **1.13** (15 mg, 0.071 mmol) in DCM (1 mL) maintained at 0 °C was treated with TPP (0.4 mg, 0.7 µmol) then irradiated by a 300 W visible light lamp while oxygen was continuously bubbled through the solution. After 0.17 h the reaction mixture was concentrated to dryness under a stream of nitrogen and the resulting

pink oil subjected to flash column chromatography (silica, 1:1 v/v PS 30-40/diethyl ether - DCM - ethyl acetate gradient elution).

Concentration of fraction **A** (R_f = 0.2 in 13:7 v/v hexane/ethyl acetate) gave the *title bisepoxide* ***5.9*** (4 mg, 16%) as a clear oil, faintly-pink due to contamination with traces of TPP.

Compound 5.9

^{1}H NMR (400 MHz) δ 7.11 (d, *J* = 7.0 Hz, 1H), 4.55 (s, 2H), 3.53 (m, 2H), 3.31 (m, 2H), 2.97 (m, 1H), 1.90 (dd, *J* = 12.0, 4.8 Hz, 2H), 1.05 (d, *J* = 12.1 Hz, 2H).

^{13}C NMR (125 MHz) δ 168.1 (CO), 136.4 (CH), 124.2 (C), 65.3 (CH_2), 49.3 (CH), 48.5 (CH), 33.9 (C), 30.9 (CH), 29.4 (CH_2), 28.1 (C).

IR ν_{max} 3069, 2927, 1752, 1660 cm^{-1}.

MS (EI, 70eV) *m/z* 244 ($M^{+\bullet}$, 65%), 171 (85), 128 (100), 115 (95).

HREIMS found: $M^{+\bullet}$, 244.0746. $C_{14}H_{12}O_4$ requires $M^{+\bullet}$, 244.0736.

mp discolouration at 140 °C, still solid at 300 °C.

Concentration of fraction **B** (R_f = 0.1 in 13:7 v/v hexane/ethyl acetate) gave the *title endo-peroxide* ***5.8*** (10 mg, 40%) as a clear oil, pale-pink due to lightly contamination with TPP.

Compound 5.8

^{1}H NMR (400 MHz) δ 7.09 (d, *J* = 7.0 Hz, 1H), 6.57 (dd, *J* = 4.5, 3.2 Hz, 2H), 5.06 (dd, *J* = 4.3, 3.2 Hz, 2H), 4.39 (s, 2H), 3.13 (m, 1H), 2.13 (dd, *J* = 12.1, 4.7 Hz, 2H), 1.10 (d, *J* = 12.1 Hz, 2H).

^{13}C NMR (100 MHz) δ 168.8 (CO), 137.4 (CH), 131.0 (CH), 125.8 (C), 74.8 (CH), 70.9 (CH_2), 37.2 (CH), 30.5 (C), 29.4 (C), 26.2 (CH_2).

IR ν_{max} 2974, 2920, 2852, 1740, 1665 cm^{-1}.

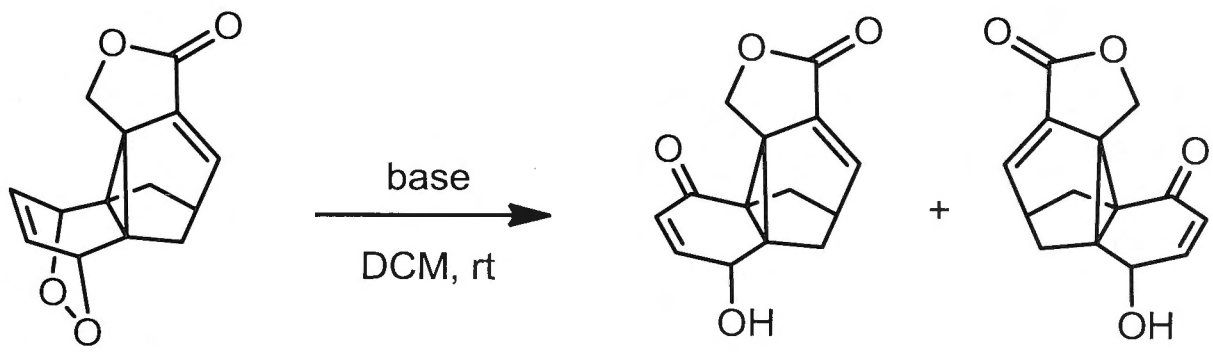
MS (EI, 70eV) *m/z* 244 ($M^{+\bullet}$, 60%), 171 (75), 128 (90), 115 (100).

HREIMS found: $M^{+\bullet}$, 244.0736. $C_{14}H_{12}O_4$ requires $M^{+\bullet}$, 244.0736.

mp discolouration at 200 °C, still solid at 300 °C.

Even under refrigeration and after thorough and repeated purification, *endo*-peroxide **5.8** rearranged, presumably in the presence of a trace of tetraphenyl porphyrin (TPP), to quantitatively yield the title bisepoxide **5.9** as a colourless solid.

(5*RS*,6a*RS*,10*SR*,10a*SR*,10b*RS*)-10-Hydroxy-5,6-dihydro-5,10a-methanobenzo[1,3]cyclopropa-[1,2-*h*]isobenzofuran-3,7(1*H*,10*H*)-dione (5.10-*R* and 5.10-*S*)



5.8 **5.10-*R*** **5.10-*S***

Achiral Method - A magnetically stirred solution of crude *endo*-peroxide **5.8** (max. 0.28 mmol) in DCM (1 mL) was treated with triethyl amine (8 µl, 20 mol%). After stirring at room temperature for 0.5 h the reaction was concentrated under a stream of nitrogen and the resulting pale-yellow oil subjected to flash column chromatography (silica, diethyl ether – DCM – ethyl acetate gradient elution) to give two fractions, A and B.

Concentration of fraction **A** (R_f = 0.3 in 2:3 v/v hexane/ethyl acetate) gave bisepoxide **5.9** (5 mg, 7%) as a colourless, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.1 in 2:3 v/v hexane/ethyl acetate) gave the racemic mixture of the *title alcohols (±)-**5.10*** (64 mg, 92%) as a colourless, crystalline solid.

Chiral Method - A magnetically stirred solution of *endo*-peroxide **5.8** (20 mg, 0.082 mmol) in DCM (1 mL) was treated with quinine-derived catalyst **5.13** (14 mg, 40 mol%) at room temperature. After 48 h the reaction was concentrated under a stream of nitrogen and the resulting yellow oil subjected to flash column chromatography (silica, diethyl ether – DCM – ethyl acetate gradient elution) to give two fractions.

Concentration of fraction **A** (R_f = 0.3 in 2:3 v/v hexane/ethyl acetate) gave bisepoxide **5.9** (12 mg, 60%) as a colourless, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction **B** (R_f = 0.1 in 2:3 v/v hexane/ethyl acetate) gave the enantioenriched mixture of the *title alcohols (±)-**5.10*** (7 mg, 35%) as a colourless, crystalline solid.

Compound (±)-5.10

^{1}H NMR (400 MHz) δ 7.26 (d, *J* = 7.0 Hz, 1H), 6.80 (dd, *J* = 10.2, 4.9 Hz, 1H), 6.12 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.72 (d, *J* = 4.9 Hz, 1H), 4.32 (s, 2H), 3.07 (m, 1H), 2.21 (dd, *J* = 12.4, 4.7 Hz, 1H), 2.01 (dd, *J* = 12.4, 4.7 Hz, 1H), 1.37 (d, *J* = 12.4 Hz, 1H), 1.16 (d, *J* = 12.4 Hz, 1H).

^{13}C NMR (100 MHz) δ 194.7 (CO), 160.6 (CO), 143.2 (CH), 138.6 (CH), 130.1 (CH), 124.4 (C), 66.4 (CH_2), 62.7 (CH), 32.3 (CH), 29.4 (C), 28.9 (CH_2), 27.5 (CH_2) (two signals due to quaternary carbons were obscured).

IR ν_{max} 3334, 2931, 1759, 1657 cm^{-1}.

MS (EI, 70eV) *m/z* 244 ($M^{+\bullet}$, 70%), 216 (55), 141 (55), 128 (50), 115 (85), 55 (100).

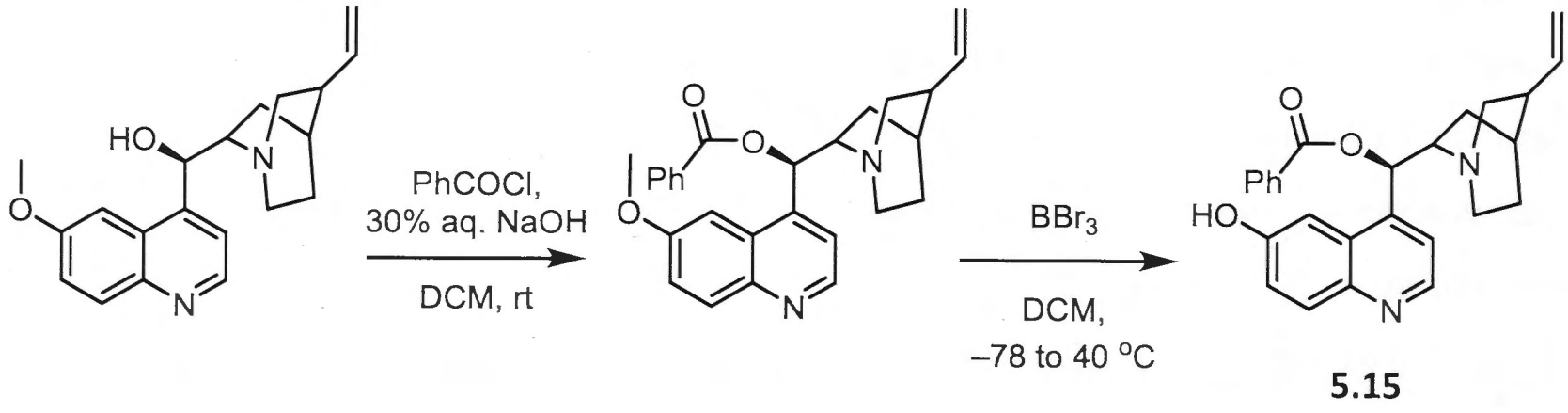
HREIMS found: $M^{+\bullet}$, 244.0747. $C_{14}H_{12}O_4$ requires $M^{+\bullet}$, 244.0736.

mp brown at 190 °C, still solid at 300 °C.

X-ray (see Appendix 10).

$[\alpha]_D$ +12 (*c* 0.1, $CDCl_3$)

Quinine-derived chiral base 5.15



5.15

Step i – The quinine-derived catalyst **5.15** was synthesised following a literature procedure.[15] To a magnetically stirred solution of quinine (324 mg, 1.00 mmol) in DCM (10 mL) were sequentially added benzoyl chloride (0.6 mL, 5.0 mmol) and NaOH (1.4 mL of a 30% w/w aq. solution) at room temperature. After 4 h of vigorous stirring the reaction mixture was partitioned between water and DCM (5 mL each), the aqueous layer extracted with DCM (2 x 5 mL) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting yellow solid to flash column chromatography (silica, 50:1 v/v ethyl acetate/NEt_3 elution) gave, after concentration of the appropriate fractions (R_f = 0.2 in 50:1 v/v ethyl acetate/NEt_3), the title intermediate *O*-benzoylquinine (407 mg, 95%) as an off-white foam.

***O*-Acylated quinine**

^{1}H NMR (400 MHz) δ 8.72 (d, *J* = 4.8 Hz, 1H), 8.10 (m, 2H), 8.02 (d, *J* = 9.3 Hz, 1H), 7.60 (m, 1H), 7.53 (m, 1H), 7.48 (m, 2H), 7.43 - 7.36 (complex m, 2H), 6.80 (broad s, 1H), 5.84 (m, 1H), 4.98 - 5.06 (complex m, 2H), 3.96 (s, 3H), 3.50 (m, 1H), 3.28 - 3.18 (complex m, 1H), 3.11 (m, 1H), 2.77 - 2.65 (complex m, 2H), 2.36 - 2.28 (broad s, 1H), 1.98 - 1.88 (complex m, 2H), 1.84 - 1.70 (complex m, 2H), 1.64 - 1.54 (complex m, 1H).

These data matched those reported by Shi *et al.*[15]

Step ii – A magnetically stirred solution of the above-mentioned *O*-benzoylquinine (407 mg, 0.956 mmol) in DCM (20 mL) maintained at –78 °C was continuously flushed with nitrogen, and treated slowly with a solution of BBr_3 (3.8 mL, 1 M solution in DCM, 3.83 mmol). The resulting

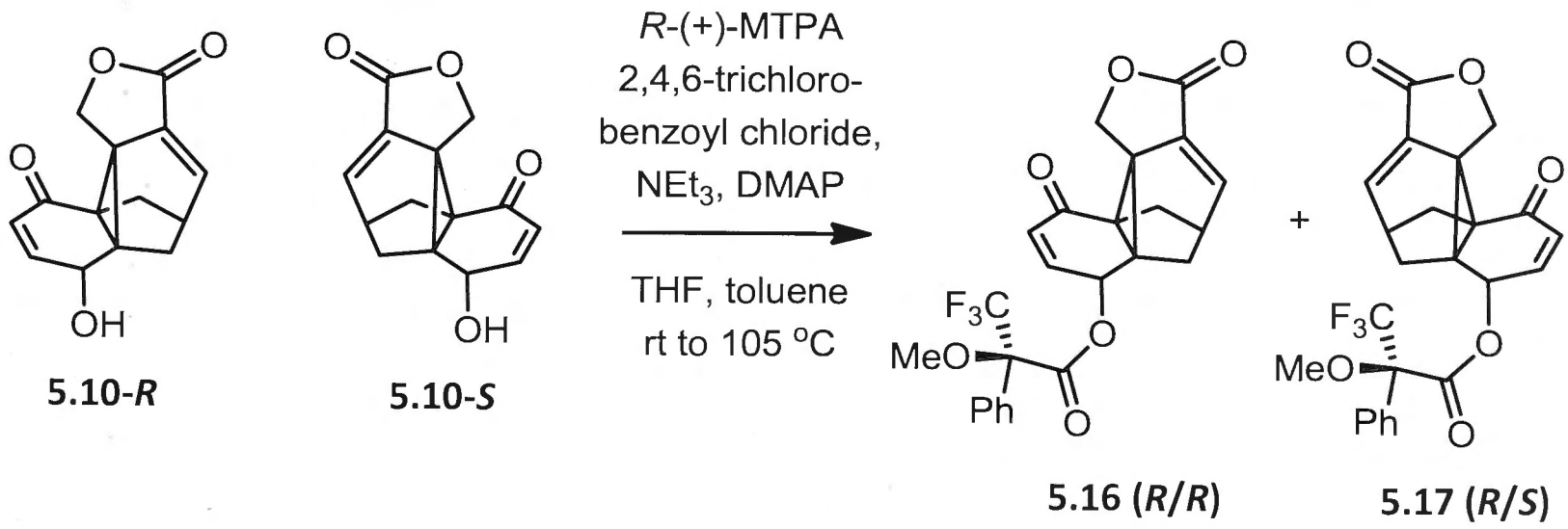
mixture was slowly allowed to warm to room temperature, heated to 40 °C for 1 h and then cooled to 0 °C. While stirring and maintaining the temperature below 5 °C, $NaHCO_3$ (10 mL of a sat aq. solution) was added slowly and stirring continued for 0.5 h. The mixture was partitioned between water and DCM (5 mL each), the aqueous layer extracted with DCM (2 x 10 mL), and the combined organic layers washed with water (1 x 5 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting solid to flash column chromatography (silica, 50:1:2 – 45:1:5 v/v/v ethyl acetate/NEt_3/MeOH gradient elution) gave, after concentration of the appropriate fractions (R_f = 0.1 in 50:1:2 v/v/v ethyl acetate/NEt_3/MeOH) the title compound **5.15** (353 mg, 89%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.4 Hz, 1H), 8.06 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 9.3 Hz, 1H), 7.78 (broad s, 1H), 7.60 - 7.28 (complex m, 5H), 6.77 (s, 1H), 5.71 (m, 1H), 4.96 - 4.87 (complex m, 2H), 3.44 - 3.14 (complex m, 4H), 3.05 - 2.91 (complex m, 1H), 2.71 - 2.53 (complex m, 2H), 2.92 - 2.19 (broad s, 1H), 1.87 - 1.69 (complex m, 2H), 1.59 - 1.45 (complex m, 1H), (the OH-signal was not observed).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.62 (d, *J* = 4.2 Hz, 1H), 8.08 - 8.05 (m, 2H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.70 - 7.65 (complex m, 1H), 7.58 - 7.49 (complex m, 4H), 7.33 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.44 (d, *J* = 7.7 Hz, 1H), 5.98 - 5.88 (complex m, 1H), 5.02 - 4.94 (complex m, 2H), 3.50 - 3.44 (complex m, 1H), 3.14 - 3.05 (complex m, 1H), 2.90 - 2.82 (complex m, 1H), 2.57 - 2.40 (complex m, 2H), 2.20 (s, 1H), 2.00 - 1.92 (complex m, 1H), 1.77 - 1.45 (complex m, 4H).

These data matched those reported by Shi *et al.*[15]

(1*R*,4a*S*,6*S*,10a*S*,10b*R*)-4,8-Dioxo-1,4,6,8-tetrahydro-5*H*,10*H*-6,10b-methanobenzo[2,3]cyclopropa[1,2-*d*]isobenzofuran-1-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (5.16) and (4a*R*,6*R*,10a*R*,10b*S*)-4,8-Dioxo-1,4,6,8-tetrahydro-5*H*,10*H*-6,10b-methanobenzo[2,3]cyclopropa[1,2-*d*]isobenzofuran-1-yl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (5.17)



Derivatisation of the Racemic Mixture of Compound 5.10 - Following a literature procedure,[16] a magnetically stirred solution of *R*-(+)-MTPA (15 mg, 0.065 mmol) and triethylamine (30 μL,

0.21 mmol) in THF (2 mL) maintained at room temperature was treated with 2,4,6-trichlorobenzoyl chloride (10 µL, 0.061 mmol) and stirred for 1.5 h, after which time it was diluted with toluene (2 mL). This solution was then added over 1 h *via* syringe pump to a magnetically stirred solution of compound **5.10** (10 mg, 0.041 mmol, racemic mixture) and DMAP (50 mg, 0.41 mmol) in toluene (4 mL) heated at 90 °C. After addition was complete the resulting mixture was heated at 105 °C for 1 h. The reaction mixture was then allowed to cool to room temperature and treated with $NaHCO_3$ (2 mL of a sat. aq. solution), extracted with ethyl acetate (2 x 2 mL), washed with NH_4Cl (2 mL of a sat. aq. solution), before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting pale yellow oil was subjected to column chromatography (basic alumina, 1:1 v/v pentane/diethyl ether – diethyl ether – DCM gradient elution) to give, after concentration of the appropriate fractions (R_f = 0.8 in 2:3 v/v hexane/ethyl acetate), the racemic mixture of the *title Mosher esters* ***5.16*** *and* ***5.17*** (7 mg, 37%) as a clear, colourless oil.

Derivatisation of the Enantioenriched Mixture of Compound 5.10 - Following a literature procedure,[16] a magnetically stirred solution of *R*-(+)-MTPA (8 mg, 0.03 mmol) and triethylamine (15 µL, 0.23 mmol) in THF (1 mL) maintained at room temperature was treated with 2,4,6-trichlorobenzoyl chloride (5 µL, 0.03 mmol) and stirred for 1.5 h, after which time it was diluted with toluene (1 mL). This solution was then added over 1 h *via* syringe pump to a magnetically stirred solution of compound **5.10** (5 mg, 0.02 mmol, enantioenriched) and DMAP (12 mg, 0.098 mmol) in toluene (2 mL) heated at 90 °C in a high pressure compatible sealable vial. After addition was complete the vial was sealed and the reaction mixture heated to 105 °C. After 1 h the reaction mixture was allowed to cool to room temperature and treated with $NaHCO_3$ (2 mL of a sat. aq. solution), extracted with ethyl acetate (2 x 2 mL), washed with NH_4Cl (2 mL of a sat. aq. solution), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude material was sensitive to column chromatography (silica or alumina) and was not purified further. Judging by ^{19}F and ^{1}H NMR, the Mosher esters **5.16** and **5.17** were obtained in a 1:2 ratio (and in quantitative yield judging by the ^{1}H NMR spectrum).

Compounds 5.16/5.17

^{1}H NMR (400 MHz)[1] δ 7.49 - 7.38$^{\#}$ (complex m, 4H), 7.26^{+} (d, *J* = 7.0 Hz, 1H), 7.23^{+} (d, *J* = 7.0 Hz, 1H), 6.81* (dd, *J* = 10.6, 5.0 Hz, 1H), 6.78 (dd, *J* = 10.6, 5.0 Hz, 1H), 6.28* (d, *J* = 10.3 Hz, 1H), 6.23 (d, *J* = 10.3 Hz, 1H), 6.01* (d, *J* = 4.8 Hz, 1H), 5.98 (d, *J* = 4.8 Hz, 1H), 4.37$^{\#}$ (q, *J* = 9.5 Hz, 2H), 3.54^{+} (d, *J* = 1.1 Hz, 3H), 3.48^{+} (d, *J* = 1.1 Hz, 3H), 3.02 (m, 1H), 2.93* (m, 1H), 1.97$^{\#}$ (dd, *J* =

[1] The asterisk (*) denotes signals due to the major diastereomer **5.17**. The plus sign ($^{+}$) denotes resonances that were partially covered in the enantioenriched crude product mixture and thus could not be assigned to one specific diastereomer. Resonances followed by a hash sign ($^{\#}$) were not differentiated by the anisotropic effect.

12.7, 5.0 Hz, 1H), 1.89 (dd, *J* = 12.4, 4.8 Hz, 1H), 1.63* (dd, *J* = 12.4, 4.8 Hz, 1H), 1.33# (dd, *J* = 12.4, 8.7 Hz, 2H), 1.08* (d, *J* = 12.4 Hz, 1H), 0.89* (d, *J* = 12.4 Hz, 1H).

^{13}C NMR (75 MHz) δ 193.5/193.4 (CO), 167.3 (CO), 165.9/165.8 (CO), 138.8/138.7 (CH), 137.5/137.4 (CH), 132.9/132.8 (CH), 131.6/131.1 (C), 130.1/130.0 (CH), 128.7 (CH), 128.6 (CH), 128.2 (C), 127.3/127.3 (CH), 127.0/126.9 (CH), 124.1/124.0 (C), 66.7/66.4 (CH), 66.2 (CH_2), 55.7/55.4 (CH_3), 38.5/38.3 (C), 37.3/37.2 (C), 35.5/35.4 (C), 32.1/32.1 (CH), 28.8/28.3 (CH_2), 27.0/27.0 (CH_2).

^{19}F NMR (300 MHz) δ −71.09 (s, 3F), −71.14 (s, 3F).

IR ν_{max} 3064, 2955, 2851, 1765, 1671, 1452, 1389, 1273, 1240, 1181, 1015 cm^{-1}.

MS (EI, 70eV) *m/z* 460 ($M^{+\bullet}$, 5%), 368 (5), 227 (15), 209 (5), 189 (100), 186 (45), 115 (10), 105 (15), 77 (10).

HREIMS found: $M^{+\bullet}$, 460.1127. $C_{24}H_{19}F_3O_6$ requires $M^{+\bullet}$, 460.1134.

6.6. References

(1) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(2) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

(3) Birch, A. J.; Fitton, P.; Smith, D. C. C.; Steere, D. E.; Stelfox, A. R. *J. Chem. Soc.* **1963**, 2209.

(4) Lombardo, L. *Org. Synth.* **1993**, *8*.

(5) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. I.

(6) Winter, B.; Gallo-Flückiger, S. *Helv. Chim. Acta* **2005**, *88*, 3118.

(7) Ksander, G. M.; deJesus, R.; Yuan, A.; Fink, C.; Moskal, M.; Carlson, E.; Kukkola, P.; Bilci, N.; Wallace, E.; Neubert, A.; Feldman, D.; Mogelesky, T.; Poirier, K.; Jeune, M.; Steele, R.; Wasvery, J.; Stephan, Z.; Cahill, E.; Webb, R.; Navarrete, A.; Lee, W.; Gibson, J.; Alexander, N.; Sharif, H.; Hospattankar, A. *J. Med. Chem.* **2001**, *44*, 4677.

(8) House, H. O.; Babad, H.; Toothill, R. B.; Noltes, A. W. *J. Org. Chem.* **1962**, *27*, 4141.

(9) Hay, M. P.; Hicks, K. O.; Pchalek, K.; Lee, H. H.; Blaser, A.; Pruijn, F. B.; Anderson, R. F.; Shinde, S. S.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **2008**, *51*, 6853.

(10) Ewing, G. D.; Paquette, L. A. *J. Org. Chem.* **1975**, *40*, 2965.

(11) Sieckmann, R.; Ger. Offen. , G. P., Ed. 1989.

(12) Ferraz, H. M. C.; Silva Jr, L. F. *Tetrahedron* **2001**, *57*, 9939.

(13) Hellwinkel, D.; Kosack, T. *Liebigs Ann. Chem.* **1985**, *1985*, 226.

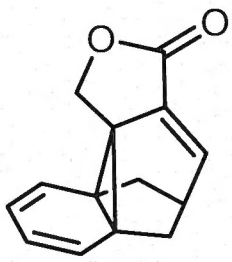
(14) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797.

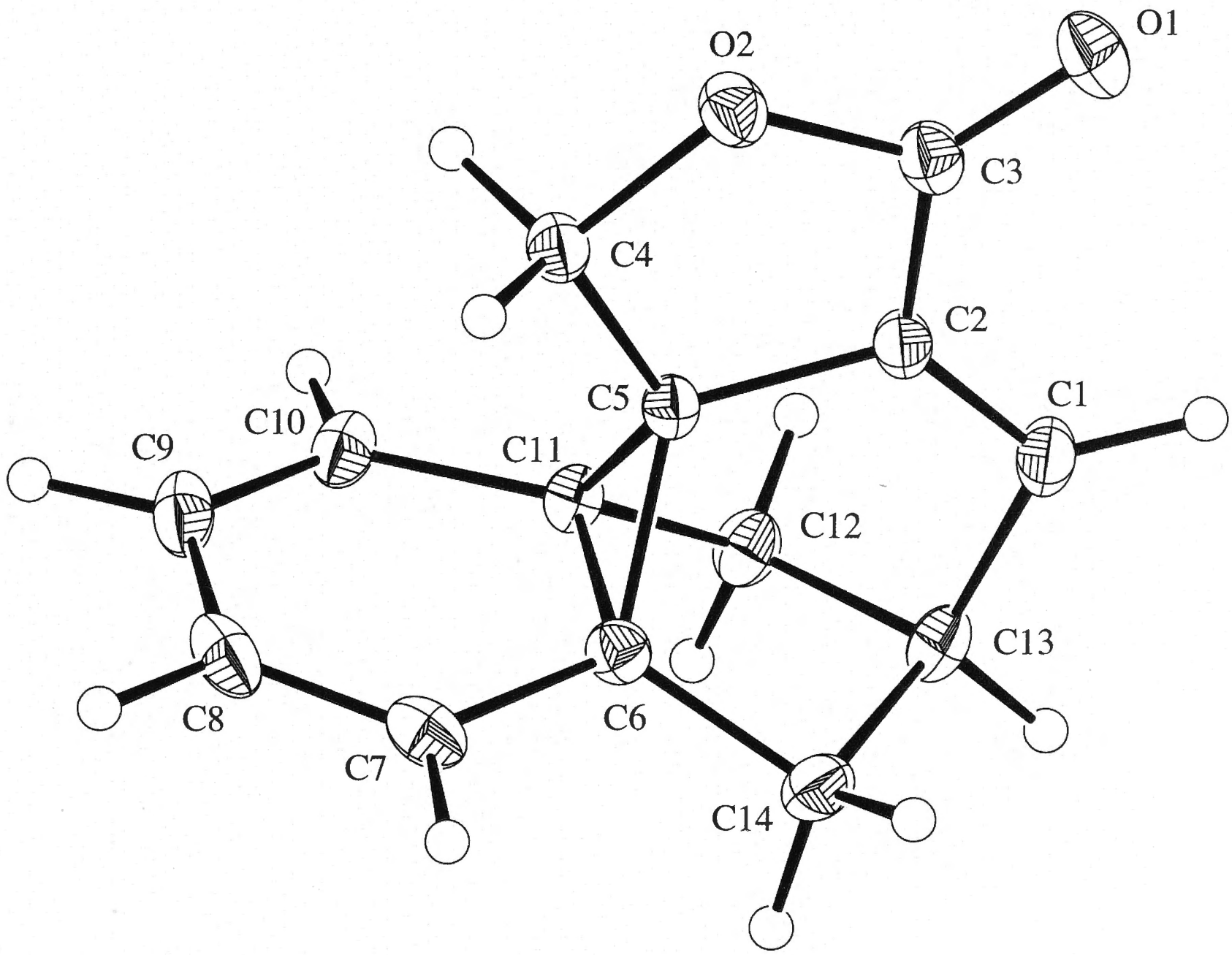
(15) Shi, M.; Lei, Z.-Y.; Zhao, M.-X.; Shi, J.-W. *Tetrahedron Lett.* **2007**, *48*, 5743.

(16) Gao, N.; Ma, X.; Petit, L.; Schwartz, B. D.; Banwell, M. G.; Willis, A. C.; Cade, I. A.; Rae, A. D. *Aust. J. Chem.* **2013**, *66*, 30.

Appendix 1

X-ray Crystal Structure Report for Compound 1.13.





Crystal structure of $C_{14}H_{12}O_2$ — ban1133

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Abstract

The crystal structure of $C_{14}H_{12}O_2$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{14}H_{12}O_2$.

Experimental

The compound was prepared by NH and crystallized from pentane/diethylether. The sample ID is NH8-16-f2.

Refinement

All H atoms were located in a difference electron density map, but were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C—H in the range 0.93–0.98Å) and with U_{iso}(H) in the range 1.2-1.5 times U_{eq} of the parent atom, after which the positions were refined without restraints and the displacement parameters were held fixed.

The largest peaks in the final difference electron density map are located midway along C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*-II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet,

pp. 307–326. New York: Academic Press.

Molecular Structure Corporation. (1992–1997). *TEXSAN*. Single Crystal Structure Analysis Software. Version 1.8. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Johnson, C. K. (1976). *ORTEP*II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.

(ban1133)

Crystal data

$C_{14}H_{12}O_2$
$M_r = 212.25$
Triclinic, $P\overline{1}$
$a = 8.0384\ (2)$ Å
$b = 8.2320\ (2)$ Å
$c = 8.7349\ (2)$ Å
$\alpha = 79.3581\ (14)°$
$\beta = 80.7333\ (17)°$
$\gamma = 65.1725\ (14)°$
$V = 513.30\ (2)$ Å^3

$Z = 2$
$F(000) = 224$
$D_x = 1.373$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 8980 reflections
$\theta = 2.6–30°$
$\mu = 0.09$ mm^{-1}
$T = 200$ K
Plate, Colourless
$0.47 \times 0.32 \times 0.09$ mm

Data collection

Nonius KappaCCD diffractometer
graphite
φ and ω scans with CCD
Absorption correction: Multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)
$T_{min} = 0.899$, $T_{max} = 0.992$
15557 measured reflections
2995 independent reflections

2512 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.026$
$\theta_{max} = 30.0°$, $\theta_{min} = 2.8°$
$h = -11 \rightarrow 11$
$k = -10 \rightarrow 11$
$l = -11 \rightarrow 12$

Refinement

Refinement on F^2
Least-squares matrix: Full
$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.101$
$S = 0.98$
2995 reflections
181 parameters
0 restraints

Primary atom site location: Structure-invariant direct methods
Hydrogen site location: Inferred from neighbouring sites
Only H-atom coordinates refined
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.05P)^2 + 0.12P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.019$
$\Delta\rho_{max} = 0.34$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.94482 (11)	0.24879 (12)	0.66387 (10)	0.0431
O2	0.78991 (11)	0.09982 (10)	0.60704 (9)	0.0350
C1	0.85689 (14)	0.45343 (15)	0.32625 (14)	0.0351
C2	0.81495 (13)	0.32256 (13)	0.41485 (12)	0.0286
C3	0.86043 (13)	0.22791 (14)	0.57224 (13)	0.0317
C4	0.68532 (15)	0.10401 (14)	0.48286 (12)	0.0303
C5	0.70835 (12)	0.24506 (12)	0.35438 (11)	0.0252
C6	0.74264 (13)	0.22663 (13)	0.17955 (11)	0.0277
C7	0.72966 (17)	0.07130 (14)	0.13135 (13)	0.0361
C8	0.57179 (18)	0.04705 (15)	0.16058 (14)	0.0396
C9	0.40139 (16)	0.18372 (15)	0.22043 (14)	0.0377
C10	0.39314 (14)	0.34076 (14)	0.25217 (12)	0.0322
C11	0.56169 (12)	0.37125 (12)	0.24540 (11)	0.0262
C12	0.57397 (14)	0.55242 (13)	0.19342 (14)	0.0324
C13	0.78498 (15)	0.50171 (15)	0.16792 (13)	0.0348
C14	0.85905 (15)	0.32471 (16)	0.09130 (13)	0.0349
H11	0.9274 (19)	0.5126 (19)	0.3624 (16)	0.0426*
H41	0.7379 (18)	−0.0203 (18)	0.4533 (15)	0.0361*
H42	0.5557 (18)	0.1333 (17)	0.5292 (15)	0.0357*
H71	0.836 (2)	−0.013 (2)	0.0782 (17)	0.0450*
H81	0.565 (2)	−0.059 (2)	0.1294 (17)	0.0484*
H91	0.287 (2)	0.1638 (19)	0.2258 (17)	0.0453*
H101	0.2748 (19)	0.4361 (19)	0.2786 (16)	0.0416*
H121	0.5153 (18)	0.6378 (18)	0.2729 (16)	0.0391*
H122	0.5188 (18)	0.6073 (18)	0.0931 (16)	0.0389*
H131	0.8151 (18)	0.6020 (19)	0.0991 (16)	0.0420*
H141	0.994 (2)	0.2542 (18)	0.1005 (16)	0.0426*
H142	0.8384 (19)	0.3511 (18)	−0.0204 (17)	0.0415*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0409 (4)	0.0475 (5)	0.0466 (5)	−0.0171 (4)	−0.0159 (3)	−0.0114 (4)
O2	0.0401 (4)	0.0368 (4)	0.0324 (4)	−0.0185 (3)	−0.0111 (3)	−0.0004 (3)
C1	0.0314 (5)	0.0373 (5)	0.0438 (6)	−0.0204 (4)	−0.0005 (4)	−0.0090 (4)
C2	0.0254 (4)	0.0306 (5)	0.0335 (5)	−0.0131 (4)	−0.0020 (3)	−0.0088 (4)
C3	0.0273 (4)	0.0321 (5)	0.0372 (5)	−0.0106 (4)	−0.0042 (4)	−0.0098 (4)
C4	0.0350 (5)	0.0304 (5)	0.0297 (5)	−0.0170 (4)	−0.0072 (4)	−0.0010 (4)
C5	0.0253 (4)	0.0248 (4)	0.0279 (4)	−0.0119 (3)	−0.0028 (3)	−0.0042 (3)
C6	0.0272 (4)	0.0266 (4)	0.0287 (4)	−0.0096 (3)	−0.0024 (3)	−0.0053 (3)
C7	0.0462 (6)	0.0289 (5)	0.0322 (5)	−0.0108 (4)	−0.0091 (4)	−0.0073 (4)
C8	0.0590 (7)	0.0307 (5)	0.0379 (6)	−0.0231 (5)	−0.0207 (5)	0.0006 (4)
C9	0.0419 (6)	0.0410 (6)	0.0392 (6)	−0.0265 (5)	−0.0176 (4)	0.0092 (4)
C10	0.0273 (4)	0.0341 (5)	0.0355 (5)	−0.0151 (4)	−0.0069 (4)	0.0048 (4)
C11	0.0241 (4)	0.0240 (4)	0.0307 (5)	−0.0105 (3)	−0.0023 (3)	−0.0022 (3)
C12	0.0322 (5)	0.0248 (4)	0.0398 (5)	−0.0131 (4)	−0.0016 (4)	−0.0008 (4)
C13	0.0347 (5)	0.0346 (5)	0.0393 (5)	−0.0214 (4)	0.0012 (4)	−0.0006 (4)
C14	0.0301 (5)	0.0418 (6)	0.0321 (5)	−0.0160 (4)	0.0033 (4)	−0.0050 (4)

Geometric parameters (Å, º)

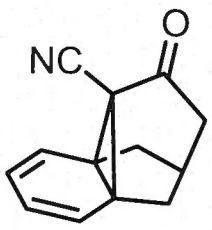
O1—C3	1.2058 (12)	C7—C8	1.3435 (17)
O2—C3	1.3615 (13)	C7—H71	0.958 (15)
O2—C4	1.4629 (12)	C8—C9	1.4518 (18)
C1—C2	1.3365 (14)	C8—H81	0.983 (15)
C1—C13	1.5054 (16)	C9—C10	1.3443 (15)
C1—H11	1.002 (14)	C9—H91	0.996 (15)
C2—C3	1.4689 (15)	C10—C11	1.4684 (13)
C2—C5	1.4661 (13)	C10—H101	0.971 (14)
C4—C5	1.5081 (13)	C11—C12	1.5163 (13)
C4—H41	0.996 (13)	C12—C13	1.5553 (14)
C4—H42	0.998 (13)	C12—H121	0.997 (14)
C5—C6	1.5317 (13)	C12—H122	0.989 (14)
C5—C11	1.5306 (13)	C13—C14	1.5585 (16)
C6—C7	1.4657 (14)	C13—H131	1.020 (14)
C6—C11	1.5470 (13)	C14—H141	0.999 (14)
C6—C14	1.5146 (14)	C14—H142	0.985 (14)
O1···C7^{i}	3.312 (1)	O2···O2^{i}	3.471 (1)
O1···C4^{i}	3.437 (1)	O2···C12^{ii}	3.600 (1)
O1···C10^{ii}	3.450 (1)	C3···C4^{i}	3.546 (1)
O1···C1^{iii}	3.458 (2)	C4···C9^{iv}	3.369 (2)
O2···C9^{iv}	3.325 (2)	C8···C8^{v}	3.521 (3)
O2···C3^{i}	3.377 (1)		
C3—O2—C4	111.98 (8)	C7—C8—H81	120.1 (9)
C2—C1—C13	112.30 (9)	C9—C8—H81	117.5 (8)
C2—C1—H11	123.4 (8)	C8—C9—C10	121.89 (10)
C13—C1—H11	124.3 (8)	C8—C9—H91	117.5 (8)
C1—C2—C3	131.90 (9)	C10—C9—H91	120.2 (8)
C1—C2—C5	120.05 (9)	C9—C10—C11	120.66 (10)
C3—C2—C5	108.03 (8)	C9—C10—H101	120.0 (8)
C2—C3—O2	108.57 (8)	C11—C10—H101	119.3 (8)
C2—C3—O1	130.26 (10)	C6—C11—C5	59.69 (6)
O2—C3—O1	121.17 (10)	C6—C11—C10	116.93 (8)
O2—C4—C5	105.09 (7)	C5—C11—C10	118.30 (8)
O2—C4—H41	106.8 (7)	C6—C11—C12	106.93 (8)
C5—C4—H41	114.4 (7)	C5—C11—C12	112.59 (8)
O2—C4—H42	107.0 (7)	C10—C11—C12	124.35 (8)
C5—C4—H42	114.3 (7)	C11—C12—C13	103.16 (8)
H41—C4—H42	108.7 (10)	C11—C12—H121	113.3 (8)
C4—C5—C2	106.17 (8)	C13—C12—H121	110.4 (8)
C4—C5—C6	124.85 (8)	C11—C12—H122	109.8 (8)
C2—C5—C6	117.30 (8)	C13—C12—H122	109.8 (8)
C4—C5—C11	125.10 (8)	H121—C12—H122	110.2 (11)
C2—C5—C11	117.46 (8)	C12—C13—C1	107.93 (9)
C6—C5—C11	60.68 (6)	C12—C13—C14	102.69 (8)
C5—C6—C7	117.78 (8)	C1—C13—C14	107.57 (9)
C5—C6—C11	59.62 (6)	C12—C13—H131	111.7 (8)

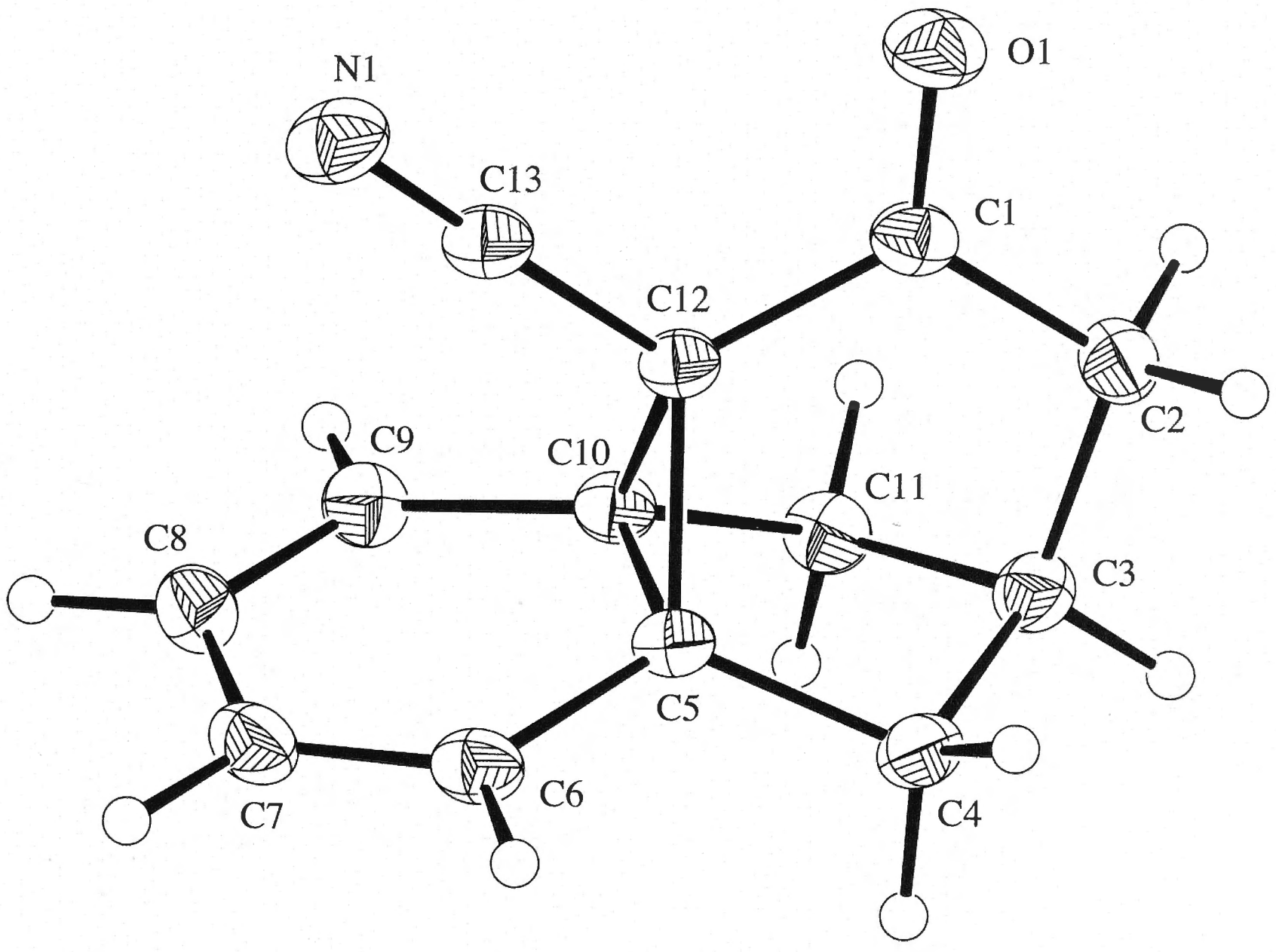
C7—C6—C11	116.83 (9)	C1—C13—H131	113.3 (8)
C5—C6—C14	112.19 (8)	C14—C13—H131	113.1 (8)
C7—C6—C14	125.04 (9)	C13—C14—C6	103.25 (8)
C11—C6—C14	107.00 (8)	C13—C14—H141	111.5 (8)
C6—C7—C8	120.76 (10)	C6—C14—H141	113.1 (8)
C6—C7—H71	118.7 (8)	C13—C14—H142	111.1 (8)
C8—C7—H71	120.6 (8)	C6—C14—H142	109.5 (8)
C7—C8—C9	121.98 (10)	H141—C14—H142	108.3 (11)
O1—C3—O2—C4	177.17 (8)	C4—C5—C11—C12	149.0 (1)
O1—C3—C2—C1	2.2 (2)	C5—C2—C1—C13	−0.7 (1)
O1—C3—C2—C5	−179.56 (9)	C5—C6—C7—C8	60.5 (1)
O2—C3—C2—C1	−177.58 (9)	C5—C6—C11—C10	−108.6 (1)
O2—C3—C2—C5	0.66 (9)	C5—C6—C11—C12	106.7 (1)
O2—C4—C5—C2	−3.45 (9)	C5—C6—C14—C13	−39.5 (1)
O2—C4—C5—C6	138.17 (9)	C5—C11—C6—C7	108.0 (1)
O2—C4—C5—C11	−145.70 (9)	C5—C11—C6—C14	−106.2 (1)
C1—C2—C5—C4	−179.70 (8)	C5—C11—C10—C9	−60.4 (1)
C1—C2—C5—C6	35.3 (1)	C5—C11—C12—C13	38.7 (1)
C1—C2—C5—C11	−34.1 (1)	C6—C5—C11—C10	106.3 (1)
C1—C13—C12—C11	−74.0 (1)	C6—C5—C11—C12	−97.02 (9)
C1—C13—C14—C6	74.5 (1)	C6—C7—C8—C9	8.7 (2)
C2—C1—C13—C12	55.5 (1)	C6—C11—C10—C9	7.9 (1)
C2—C1—C13—C14	−54.7 (1)	C6—C11—C12—C13	−24.9 (1)
C2—C3—O2—C4	−3.0 (1)	C6—C14—C13—C12	−39.2 (1)
C2—C5—C6—C7	145.81 (9)	C7—C6—C5—C11	−106.4 (1)
C2—C5—C6—C11	−107.78 (9)	C7—C6—C11—C10	−0.6 (1)
C2—C5—C6—C14	−10.5 (1)	C7—C6—C11—C12	−145.32 (9)
C2—C5—C11—C6	107.5 (1)	C7—C6—C14—C13	166.29 (9)
C2—C5—C11—C10	−146.15 (9)	C7—C8—C9—C10	−1.1 (2)
C2—C5—C11—C12	10.5 (1)	C8—C7—C6—C11	−7.5 (1)
C3—O2—C4—C5	4.09 (9)	C8—C7—C6—C14	−146.5 (1)
C3—C2—C1—C13	177.41 (9)	C8—C9—C10—C11	−7.5 (2)
C3—C2—C5—C4	1.82 (9)	C9—C10—C11—C12	145.9 (1)
C3—C2—C5—C6	−143.19 (7)	C10—C11—C6—C14	145.23 (9)
C3—C2—C5—C11	147.46 (8)	C10—C11—C12—C13	−166.3 (1)
C4—C5—C6—C7	8.0 (1)	C11—C5—C6—C14	97.30 (9)
C4—C5—C6—C11	114.4 (1)	C11—C6—C14—C13	24.0 (1)
C4—C5—C6—C14	−148.33 (9)	C11—C12—C13—C14	39.5 (1)
C4—C5—C11—C6	−114.0 (1)	C12—C11—C6—C14	0.5 (1)
C4—C5—C11—C10	−7.6 (1)		

Symmetry codes: (i) $-x+2, -y, -z+1$; (ii) $-x+1, -y+1, -z+1$; (iii) $-x+2, -y+1, -z+1$; (iv) $-x+1, -y, -z+1$; (v) $-x+1, -y, -z$.

Appendix 2

X-ray Crystal Structure Report for Compound 2.37.





Crystal structure of $C_{13}H_{11}NO$ — cade001_service

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Abstract

The crystal structure of $C_{13}H_{11}NO$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{13}H_{11}NO$.

Experimental

The compound was prepared by NH. The sample ID is NH4_81f3.

Refinement

All H atoms were located in a subsequent difference electron density map and were included at calculated positions. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C—H in the range 0.93–0.98 Å) and with U_{iso}(H) in the range 1.2-1.5 times U_{eq} of the parent atom, after which the positions were refined with riding constraints and the displacement parameters were held fixed.

The largest peaks in the final difference electron density map are located midway along C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*-II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Mackay, S., Gilmore, C. J., Edwards, C., Stewart, N. & Shankland, K. (2000). *maXus* Computer Program for the Solution and Refinement of Crystal Structures. Nonius, The Netherlands, MacScience, Japan & The University of Glasgow.

Coppens, P. (1970). The Evaluation of Absorption and Extinction in Single-Crystal Structure Analysis. Crystallographic Computing. F. R. Ahmed, S. R. Hall and C. P. Huber, eds., Munksgaard. Copenhagen. pp 255-270.

Molecular Structure Corporation. (1992–1997). *TEXSAN*. Single Crystal Structure Analysis Software. Version 1.8. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Johnson, C. K. (1976). *ORTEP*II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.

(Cade001_service)

Crystal data

$C_{13}H_{11}NO$
$M_r = 197.24$
Triclinic, $P\bar{1}$
$a = 6.7916$ (3) Å
$b = 8.2851$ (3) Å
$c = 9.0747$ (3) Å
$\alpha = 75.690$ (3)°
$\beta = 83.678$ (2)°
$\gamma = 88.747$ (2)°
$V = 491.76$ (3) Å^3
$Z = 2$
$F(000) = 208$
$D_x = 1.332$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 5971 reflections
$\theta = 3$–27.5°
$\mu = 0.09$ mm^{-1}
$T = 200$ K
Plate, Colourless
0.29 × 0.21 × 0.07 mm

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
φ and ω scans with CCD
Absorption correction: Integration via Gaussian method (Coppens, 1970) implemented in *maXus* (2000)
$T_{min} = 0.984$, $T_{max} = 0.995$
9814 measured reflections
2236 independent reflections
1812 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.035$
$\theta_{max} = 27.5°$, $\theta_{min} = 3.0°$
$h = -8 \rightarrow 8$
$k = -10 \rightarrow 10$
$l = -11 \rightarrow 11$

Refinement

Refinement on F^2
Least-squares matrix: Full
$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.098$
$S = 0.98$
2233 reflections
136 parameters
0 restraints
Primary atom site location: Direct
Hydrogen site location: Difference Fourier map
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.05P)^2 + 0.11P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.0004$
$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.20$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	y	z	U_{iso}*/U_{eq}
C1	0.22947 (17)	0.39609 (15)	−0.00585 (14)	0.0350
C2	0.2059 (2)	0.23350 (16)	−0.04739 (14)	0.0402
C3	0.20390 (19)	0.08835 (15)	0.09422 (14)	0.0382
C4	0.39609 (19)	0.09502 (15)	0.16787 (15)	0.0387
C5	0.35359 (17)	0.22910 (14)	0.25396 (13)	0.0314
C6	0.47289 (19)	0.25281 (16)	0.37241 (15)	0.0388
C7	0.3874 (2)	0.29806 (16)	0.49595 (15)	0.0433
C8	0.1743 (2)	0.31551 (17)	0.52243 (15)	0.0434
C9	0.05196 (19)	0.28463 (16)	0.42668 (14)	0.0387
C10	0.13185 (17)	0.24392 (14)	0.28329 (13)	0.0308
C11	0.03866 (18)	0.11834 (15)	0.21455 (14)	0.0369

C12	0.24983 (16)	0.38459 (13)	0.15821 (13)	0.0306
C13	0.27210 (18)	0.54266 (15)	0.19407 (14)	0.0359
N1	0.28795 (18)	0.66983 (14)	0.22040 (15)	0.0491
O1	0.23120 (15)	0.53034 (12)	−0.09824 (10)	0.0493
H21	0.3178	0.2231	−0.1247	0.0497*
H22	0.0796	0.2387	−0.0946	0.0491*
H31	0.1864	−0.0219	0.0676	0.0456*
H42	0.5157	0.1227	0.0884	0.0470*
H41	0.4163	−0.0121	0.2417	0.0465*
H61	0.6114	0.2341	0.3592	0.0483*
H71	0.4688	0.3168	0.5710	0.0525*
H81	0.1175	0.3462	0.6154	0.0522*
H91	−0.0890	0.2893	0.4496	0.0470*
H111	0.0075	0.0173	0.2944	0.0454*
H112	−0.0863	0.1601	0.1682	0.0431*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0288 (6)	0.0371 (6)	0.0351 (6)	0.0025 (5)	−0.0014 (5)	−0.0024 (5)
C2	0.0414 (7)	0.0451 (7)	0.0356 (6)	0.0023 (5)	−0.0069 (5)	−0.0118 (5)
C3	0.0419 (7)	0.0321 (6)	0.0432 (7)	0.0012 (5)	−0.0099 (5)	−0.0122 (5)
C4	0.0393 (7)	0.0329 (6)	0.0452 (7)	0.0070 (5)	−0.0087 (5)	−0.0109 (5)
C5	0.0301 (6)	0.0268 (5)	0.0358 (6)	0.0012 (4)	−0.0062 (5)	−0.0040 (4)
C6	0.0338 (6)	0.0370 (6)	0.0453 (7)	0.0010 (5)	−0.0128 (5)	−0.0062 (5)
C7	0.0485 (8)	0.0425 (7)	0.0408 (7)	−0.0007 (6)	−0.0181 (6)	−0.0081 (6)
C8	0.0517 (8)	0.0442 (7)	0.0334 (6)	0.0009 (6)	−0.0037 (5)	−0.0085 (5)
C9	0.0360 (7)	0.0401 (7)	0.0370 (6)	−0.0017 (5)	0.0004 (5)	−0.0060 (5)
C10	0.0298 (6)	0.0277 (6)	0.0329 (6)	−0.0022 (4)	−0.0037 (4)	−0.0031 (4)
C11	0.0371 (6)	0.0317 (6)	0.0410 (7)	−0.0071 (5)	−0.0064 (5)	−0.0054 (5)
C12	0.0296 (6)	0.0256 (5)	0.0349 (6)	−0.0003 (4)	−0.0045 (4)	−0.0040 (4)
C13	0.0329 (6)	0.0306 (6)	0.0417 (7)	−0.0009 (5)	−0.0065 (5)	−0.0029 (5)
N1	0.0513 (7)	0.0320 (6)	0.0652 (8)	−0.0016 (5)	−0.0142 (6)	−0.0109 (5)
O1	0.0565 (6)	0.0422 (5)	0.0397 (5)	0.0048 (4)	−0.0007 (4)	0.0056 (4)

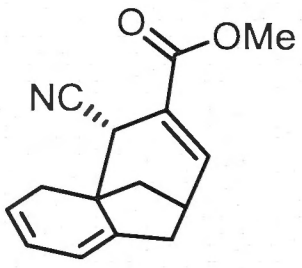
Geometric parameters (Å, º)

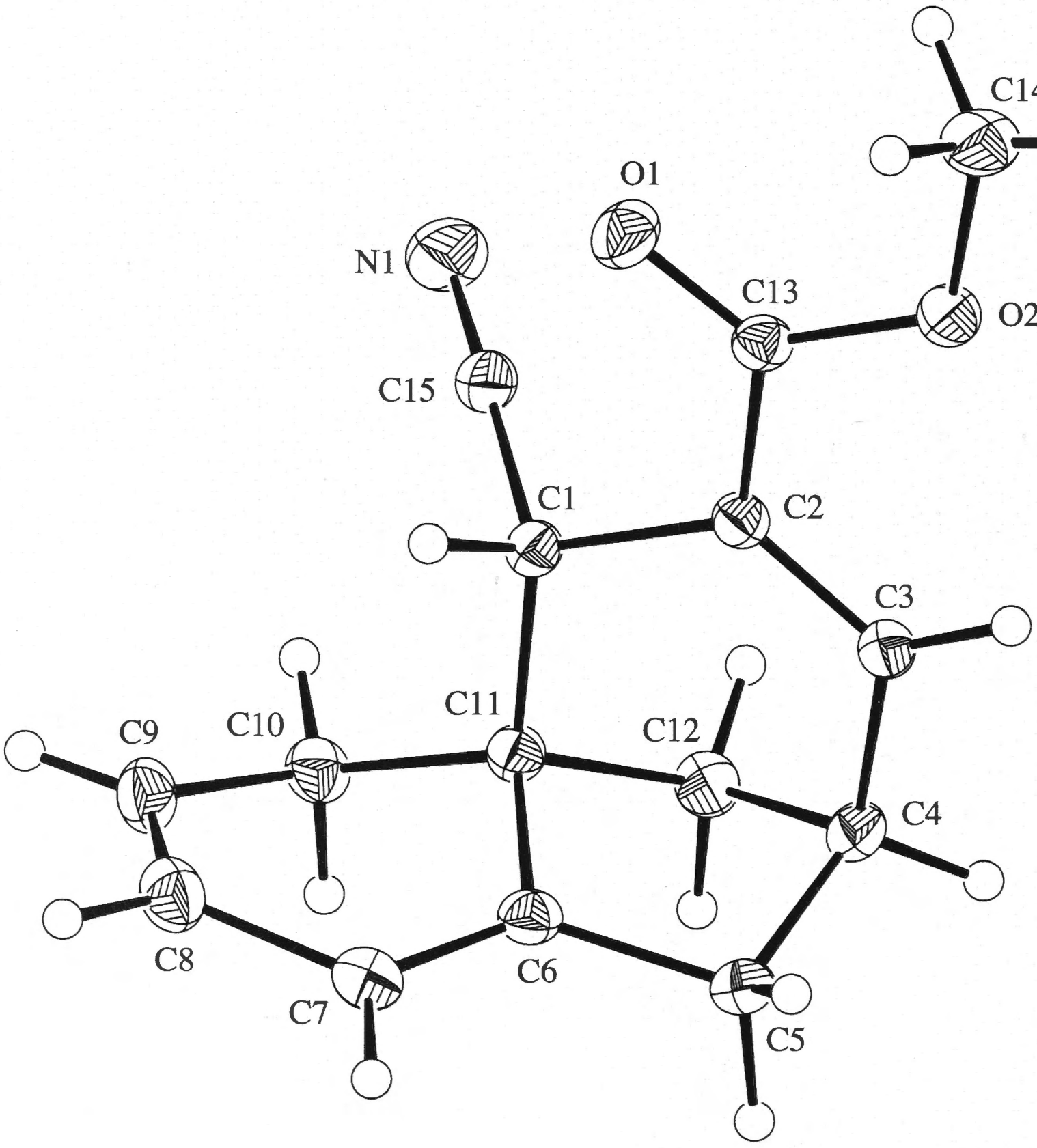
C1—C2	1.5021 (17)	C6—C7	1.3378 (19)
C1—C12	1.4897 (17)	C6—H61	0.949
C1—O1	1.2156 (15)	C7—C8	1.450 (2)
C2—C3	1.5267 (18)	C7—H71	0.966
C2—H21	0.994	C8—C9	1.3378 (18)
C2—H22	0.995	C8—H81	0.978
C3—C4	1.5385 (17)	C9—C10	1.4679 (17)
C3—C11	1.5380 (18)	C9—H91	0.959
C3—H31	1.013	C10—C11	1.5195 (16)
C4—C5	1.5143 (16)	C10—C12	1.5733 (15)
C4—H42	1.015	C11—H111	0.972
C4—H41	0.988	C11—H112	1.005
C5—C6	1.4675 (16)	C12—C13	1.4401 (16)
C5—C10	1.5078 (16)	C13—N1	1.1463 (16)
C5—C12	1.5662 (15)		
C2—C1—C12	115.90 (10)	C7—C6—H61	121.3
C2—C1—O1	123.15 (11)	C6—C7—C8	121.67 (11)
C12—C1—O1	120.94 (11)	C6—C7—H71	119.4

C1—C2—C3	110.54 (10)	C8—C7—H71	118.9
C1—C2—H21	107.9	C7—C8—C9	122.15 (12)
C3—C2—H21	110.8	C7—C8—H81	119.1
C1—C2—H22	107.4	C9—C8—H81	118.7
C3—C2—H22	111.1	C8—C9—C10	120.31 (12)
H21—C2—H22	108.9	C8—C9—H91	121.0
C2—C3—C4	108.44 (11)	C10—C9—H91	118.7
C2—C3—C11	108.44 (10)	C5—C10—C9	117.51 (10)
C4—C3—C11	104.32 (10)	C5—C10—C11	107.51 (10)
C2—C3—H31	111.1	C9—C10—C11	124.13 (10)
C4—C3—H31	112.3	C5—C10—C12	61.06 (7)
C11—C3—H31	111.9	C9—C10—C12	117.42 (10)
C3—C4—C5	102.98 (9)	C11—C10—C12	112.37 (9)
C3—C4—H42	111.9	C3—C11—C10	102.99 (9)
C5—C4—H42	112.4	C3—C11—H111	111.3
C3—C4—H41	110.1	C10—C11—H111	108.8
C5—C4—H41	109.1	C3—C11—H112	112.2
H42—C4—H41	110.2	C10—C11—H112	113.0
C4—C5—C6	123.02 (10)	H111—C11—H112	108.5
C4—C5—C10	107.86 (9)	C5—C12—C10	57.41 (7)
C6—C5—C10	117.54 (10)	C5—C12—C1	119.32 (10)
C4—C5—C12	112.50 (9)	C10—C12—C1	118.51 (9)
C6—C5—C12	118.40 (10)	C5—C12—C13	118.16 (10)
C10—C5—C12	61.53 (7)	C10—C12—C13	117.36 (10)
C5—C6—C7	120.54 (11)	C1—C12—C13	114.46 (10)
C5—C6—H61	118.2	C12—C13—N1	178.75 (13)

Appendix 3

X-ray Crystal Structure Report for Compound 2.72.





Crystal structure of $C_{15}H_{15}NO_2$ — ban1203

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The crystal structure of $C_{15}H_{15}NO_2$ is reported.

Experimental

Crystal data

$C_{15}H_{15}NO_2$
$M_r = 241.29$
Monoclinic, $C2/c$
$a = 20.7142$ (5) Å
$b = 7.7593$ (1) Å
$c = 15.8461$ (4) Å
$\beta = 105.3732$ (12)°
$V = 2455.78$ (9) Å^3
$Z = 8$
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$\mu = 0.09$ mm^{-1}
$T = 200$ K
0.42 × 0.13 × 0.08 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: Integration via Gaussian method (Coppens, 1970) implemented in *maXus* (2000)
$T_{min} = 0.976$, $T_{max} = 0.994$
23910 measured reflections
2816 independent reflections
2348 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.047$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.139$
$S = 1.02$
2810 reflections
208 parameters
0 restraints
Only H-atom coordinates refined
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.25$ e Å^{-3}

Table 1

Selected geometric parameters (Å, °)

O1—C13	1.206 (2)	C4—C5	1.549 (3)
O2—C13	1.340 (2)	C4—C12	1.532 (3)
O2—C14	1.445 (2)	C5—C6	1.510 (3)
N1—C15	1.143 (3)	C6—C7	1.333 (3)
C1—C2	1.524 (2)	C6—C11	1.526 (3)
C1—C11	1.567 (2)	C7—C8	1.467 (3)
C1—C15	1.475 (3)	C8—C9	1.345 (3)
C2—C3	1.326 (3)	C9—C10	1.498 (3)
C2—C13	1.486 (2)	C10—C11	1.523 (3)
C3—C4	1.503 (3)	C11—C12	1.532 (3)
C13—O2—C14	115.88 (16)	C6—C7—C8	119.61 (19)
C2—C1—C11	111.57 (14)	C7—C8—C9	120.2 (2)
C2—C1—C15	110.28 (14)	C8—C9—C10	120.4 (2)
C11—C1—C15	111.06 (15)	C9—C10—C11	111.37 (17)
C1—C2—C3	121.98 (16)	C6—C11—C10	109.69 (15)

C1—C2—C13	115.07 (15)	C6—C11—C1	107.37 (14)
C3—C2—C13	122.90 (16)	C10—C11—C1	111.25 (15)
C2—C3—C4	121.47 (17)	C6—C11—C12	102.46 (15)
C3—C4—C5	107.82 (16)	C10—C11—C12	117.37 (16)
C3—C4—C12	109.00 (15)	C1—C11—C12	107.97 (14)
C5—C4—C12	102.65 (16)	C4—C12—C11	101.01 (15)
C4—C5—C6	102.49 (15)	C2—C13—O2	113.42 (15)
C5—C6—C7	129.84 (19)	C2—C13—O1	123.34 (17)
C5—C6—C11	109.35 (16)	O2—C13—O1	123.24 (17)
C7—C6—C11	120.79 (18)	C1—C15—N1	178.5 (2)

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*-II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Mackay, S., Gilmore, C. J., Edwards, C., Stewart, N. & Shankland, K. (2000). *maXus* Computer Program for the Solution and Refinement of Crystal Structures. Nonius, The Netherlands, MacScience, Japan & The University of Glasgow.

Coppens, P. (1970). The Evaluation of Absorption and Extinction in Single-Crystal Structure Analysis. Crystallographic Computing. F. R. Ahmed, S. R. Hall and C. P. Huber, eds., Munksgaard. Copenhagen. pp 255-270.

Molecular Structure Corporation. (1992–1997). *TEXSAN*. Single Crystal Structure Analysis Software. Version 1.8. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Johnson, C. K. (1976). *ORTEP*II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.

Crystal structure of $C_{15}H_{15}NO_2$ — ban1203

Nora Heinrich, Martin G. Banwell and Anthony C. Willis*

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{15}H_{15}NO_2$.

Experimental

The compound was prepared by NH and crystallized from pentane/ether. The sample ID is NH7-82-f1.

Refinement

All H atoms were located in a subsequent difference electron density map and were included at calculated positions. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C—H in the range 0.93–0.98 Å) and with U_{iso}(H) in the range 1.2-1.5 times U_{eq} of the parent atom, after which the positions were refined freely and the displacement parameters were held fixed.

The largest peaks in the final difference electron density map are located midway along C—C bonds.

(ban1203)

Crystal data

$C_{15}H_{15}NO_2$	$F(000) = 1024$
$M_r = 241.29$	$D_x = 1.305$ Mg m^{-3}
Monoclinic, $C2/c$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 20.7142$ (5) Å	Cell parameters from 13727 reflections
$b = 7.7593$ (1) Å	$\theta = 2.6$–$27.5°$
$c = 15.8461$ (4) Å	$\mu = 0.09$ mm^{-1}
$\beta = 105.3732$ (12)°	$T = 200$ K
$V = 2455.78$ (9) Å^3	Rod, Colourless
$Z = 8$	0.42 × 0.13 × 0.08 mm

Data collection

Nonius KappaCCD diffractometer	2348 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.047$
φ and ω scans with CCD	$\theta_{max} = 27.5°$, $\theta_{min} = 2.7°$
Absorption correction: Integration via Gaussian method (Coppens, 1970) implemented in *maXus* (2000)	$h = -24 \rightarrow 26$
$T_{min} = 0.976$, $T_{max} = 0.994$	$k = -10 \rightarrow 8$
23910 measured reflections	$l = -20 \rightarrow 20$
2816 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.050$	Only H-atom coordinates refined
$wR(F^2) = 0.139$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.05P)^2 + 4.7P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$

$S = 1.02$	$(\Delta/\sigma)_{max} = 0.013$
2810 reflections	$\Delta\rho_{max} = 0.28$ e Å^{-3}
208 parameters	$\Delta\rho_{min} = -0.25$ e Å^{-3}
0 restraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.60408 (8)	0.44687 (19)	0.57184 (9)	0.0422
O2	0.54140 (7)	0.20901 (18)	0.56411 (8)	0.0351
N1	0.57690 (11)	0.7495 (2)	0.73076 (14)	0.0507
C1	0.64141 (9)	0.4559 (2)	0.75639 (11)	0.0266
C2	0.59884 (9)	0.3119 (2)	0.70429 (11)	0.0259
C3	0.58001 (9)	0.1765 (2)	0.74294 (12)	0.0285
C4	0.60001 (10)	0.1570 (3)	0.84084 (12)	0.0321
C5	0.67367 (11)	0.0946 (3)	0.86863 (13)	0.0349
C6	0.71222 (9)	0.2594 (2)	0.86760 (11)	0.0296
C7	0.77738 (10)	0.2833 (3)	0.87642 (13)	0.0348
C8	0.80392 (11)	0.4590 (3)	0.87903 (14)	0.0401
C9	0.76765 (11)	0.5934 (3)	0.89451 (14)	0.0398
C10	0.69998 (10)	0.5650 (3)	0.90934 (13)	0.0339
C11	0.66442 (9)	0.4124 (2)	0.85646 (11)	0.0271
C12	0.60440 (10)	0.3360 (3)	0.88287 (13)	0.0334
C13	0.58253 (9)	0.3316 (2)	0.60765 (12)	0.0274
C14	0.52245 (14)	0.2240 (3)	0.46985 (13)	0.0454
C15	0.60463 (10)	0.6207 (2)	0.74097 (13)	0.0338
H11	0.6822 (11)	0.476 (3)	0.7355 (13)	0.0317*
H31	0.5548 (11)	0.089 (3)	0.7069 (14)	0.0346*
H41	0.5690 (11)	0.081 (3)	0.8605 (14)	0.0368*
H51	0.6847 (12)	0.047 (3)	0.9293 (16)	0.0434*
H52	0.6842 (12)	0.003 (3)	0.8279 (16)	0.0423*
H71	0.8086 (12)	0.190 (3)	0.8823 (15)	0.0431*
H81	0.8492 (13)	0.472 (3)	0.8716 (16)	0.0480*
H91	0.7846 (13)	0.702 (3)	0.9006 (16)	0.0488*
H101	0.7080 (12)	0.533 (3)	0.9714 (16)	0.0424*
H102	0.6722 (12)	0.667 (3)	0.8973 (15)	0.0408*
H121	0.6146 (11)	0.319 (3)	0.9505 (15)	0.0395*
H122	0.5636 (12)	0.402 (3)	0.8593 (15)	0.0404*
H141	0.4897 (15)	0.126 (4)	0.4493 (19)	0.0677*
H142	0.5648 (16)	0.220 (4)	0.4494 (19)	0.0690*
H143	0.5049 (15)	0.334 (4)	0.452 (2)	0.0692*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0568 (10)	0.0386 (8)	0.0297 (7)	−0.0118 (7)	0.0088 (6)	0.0036 (6)
O2	0.0422 (8)	0.0328 (7)	0.0263 (6)	−0.0056 (6)	0.0023 (6)	−0.0011 (5)
N1	0.0581 (12)	0.0313 (10)	0.0568 (12)	0.0070 (9)	0.0048 (10)	−0.0004 (9)
C1	0.0283 (9)	0.0244 (8)	0.0268 (9)	−0.0008 (7)	0.0066 (7)	0.0007 (7)
C2	0.0258 (9)	0.0251 (8)	0.0256 (8)	0.0009 (7)	0.0050 (7)	−0.0009 (7)
C3	0.0274 (9)	0.0268 (9)	0.0297 (9)	−0.0009 (7)	0.0049 (7)	−0.0001 (7)
C4	0.0356 (10)	0.0310 (9)	0.0297 (9)	−0.0054 (8)	0.0086 (8)	0.0055 (8)
C5	0.0391 (11)	0.0308 (10)	0.0307 (10)	−0.0015 (8)	0.0022 (8)	0.0065 (8)
C6	0.0333 (9)	0.0300 (9)	0.0240 (8)	0.0014 (7)	0.0047 (7)	0.0014 (7)
C7	0.0323 (10)	0.0394 (11)	0.0319 (10)	0.0045 (8)	0.0067 (8)	0.0002 (8)

C8	0.0335 (10)	0.0487 (12)	0.0385 (11)	−0.0065 (9)	0.0102 (9)	−0.0015 (9)
C9	0.0411 (12)	0.0385 (11)	0.0372 (11)	−0.0119 (9)	0.0058 (9)	−0.0056 (9)
C10	0.0368 (10)	0.0320 (10)	0.0307 (10)	−0.0012 (8)	0.0049 (8)	−0.0054 (8)
C11	0.0293 (9)	0.0273 (9)	0.0243 (8)	−0.0012 (7)	0.0063 (7)	0.0001 (7)
C12	0.0333 (10)	0.0394 (11)	0.0288 (9)	−0.0022 (8)	0.0105 (8)	−0.0004 (8)
C13	0.0286 (9)	0.0245 (8)	0.0282 (9)	0.0034 (7)	0.0061 (7)	0.0000 (7)
C14	0.0639 (15)	0.0420 (12)	0.0247 (10)	−0.0037 (11)	0.0020 (9)	−0.0023 (9)
C15	0.0384 (11)	0.0270 (9)	0.0324 (10)	−0.0033 (8)	0.0031 (8)	−0.0003 (8)

Geometric parameters (Å, º)

O1—C13	1.206 (2)	C6—C7	1.333 (3)
O2—C13	1.340 (2)	C6—C11	1.526 (3)
O2—C14	1.445 (2)	C7—C8	1.467 (3)
N1—C15	1.143 (3)	C7—H71	0.96 (2)
C1—C2	1.524 (2)	C8—C9	1.345 (3)
C1—C11	1.567 (2)	C8—H81	0.98 (3)
C1—C15	1.475 (3)	C9—C10	1.498 (3)
C1—H11	1.00 (2)	C9—H91	0.91 (3)
C2—C3	1.326 (3)	C10—C11	1.523 (3)
C2—C13	1.486 (2)	C10—H101	0.99 (2)
C3—C4	1.503 (3)	C10—H102	0.97 (2)
C3—H31	0.95 (2)	C11—C12	1.532 (3)
C4—C5	1.549 (3)	C12—H121	1.04 (2)
C4—C12	1.532 (3)	C12—H122	0.97 (2)
C4—H41	0.98 (2)	C14—H141	1.01 (3)
C5—C6	1.510 (3)	C14—H142	1.01 (3)
C5—H51	1.00 (2)	C14—H143	0.94 (3)
C5—H52	1.02 (2)		
O1···C12^{i}	3.437 (3)	N1···C14^{iii}	3.304 (3)
O1···C7^{ii}	3.528 (3)	N1···C3^{vi}	3.319 (2)
O1···C14^{iii}	3.593 (3)	N1···N1^{iv}	3.399 (5)
O2···C12^{iv}	3.485 (3)	N1···C4^{vi}	3.582 (3)
O2···C14^{v}	3.599 (3)	C3···C3^{iv}	3.381 (4)
C13—O2—C14	115.88 (16)	C9—C8—H81	122.7 (15)
C2—C1—C11	111.57 (14)	C8—C9—C10	120.4 (2)
C2—C1—C15	110.28 (14)	C8—C9—H91	121.4 (16)
C11—C1—C15	111.06 (15)	C10—C9—H91	118.1 (16)
C2—C1—H11	110.7 (12)	C9—C10—C11	111.37 (17)
C11—C1—H11	108.2 (12)	C9—C10—H101	106.1 (14)
C15—C1—H11	104.9 (12)	C11—C10—H101	106.2 (14)
C1—C2—C3	121.98 (16)	C9—C10—H102	112.3 (14)
C1—C2—C13	115.07 (15)	C11—C10—H102	110.7 (14)
C3—C2—C13	122.90 (16)	H101—C10—H102	109.8 (19)
C2—C3—C4	121.47 (17)	C6—C11—C10	109.69 (15)
C2—C3—H31	118.2 (13)	C6—C11—C1	107.37 (14)
C4—C3—H31	120.3 (13)	C10—C11—C1	111.25 (15)
C3—C4—C5	107.82 (16)	C6—C11—C12	102.46 (15)
C3—C4—C12	109.00 (15)	C10—C11—C12	117.37 (16)
C5—C4—C12	102.65 (16)	C1—C11—C12	107.97 (14)
C3—C4—H41	111.3 (13)	C4—C12—C11	101.01 (15)
C5—C4—H41	113.6 (13)	C4—C12—H121	107.7 (13)
C12—C4—H41	112.0 (13)	C11—C12—H121	111.7 (12)

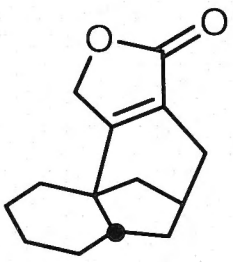
C4—C5—C6	102.49 (15)	C4—C12—H122	111.3 (14)
C4—C5—H51	110.3 (14)	C11—C12—H122	112.1 (14)
C6—C5—H51	109.9 (14)	H121—C12—H122	112.3 (18)
C4—C5—H52	113.4 (13)	C2—C13—O2	113.42 (15)
C6—C5—H52	112.2 (13)	C2—C13—O1	123.34 (17)
H51—C5—H52	108.5 (19)	O2—C13—O1	123.24 (17)
C5—C6—C7	129.84 (19)	O2—C14—H141	104.3 (17)
C5—C6—C11	109.35 (16)	O2—C14—H142	107.9 (17)
C7—C6—C11	120.79 (18)	H141—C14—H142	116 (2)
C6—C7—C8	119.61 (19)	O2—C14—H143	111.3 (18)
C6—C7—H71	122.8 (14)	H141—C14—H143	114 (2)
C8—C7—H71	117.6 (14)	H142—C14—H143	103 (2)
C7—C8—C9	120.2 (2)	C1—C15—N1	178.5 (2)
C7—C8—H81	117.1 (15)		

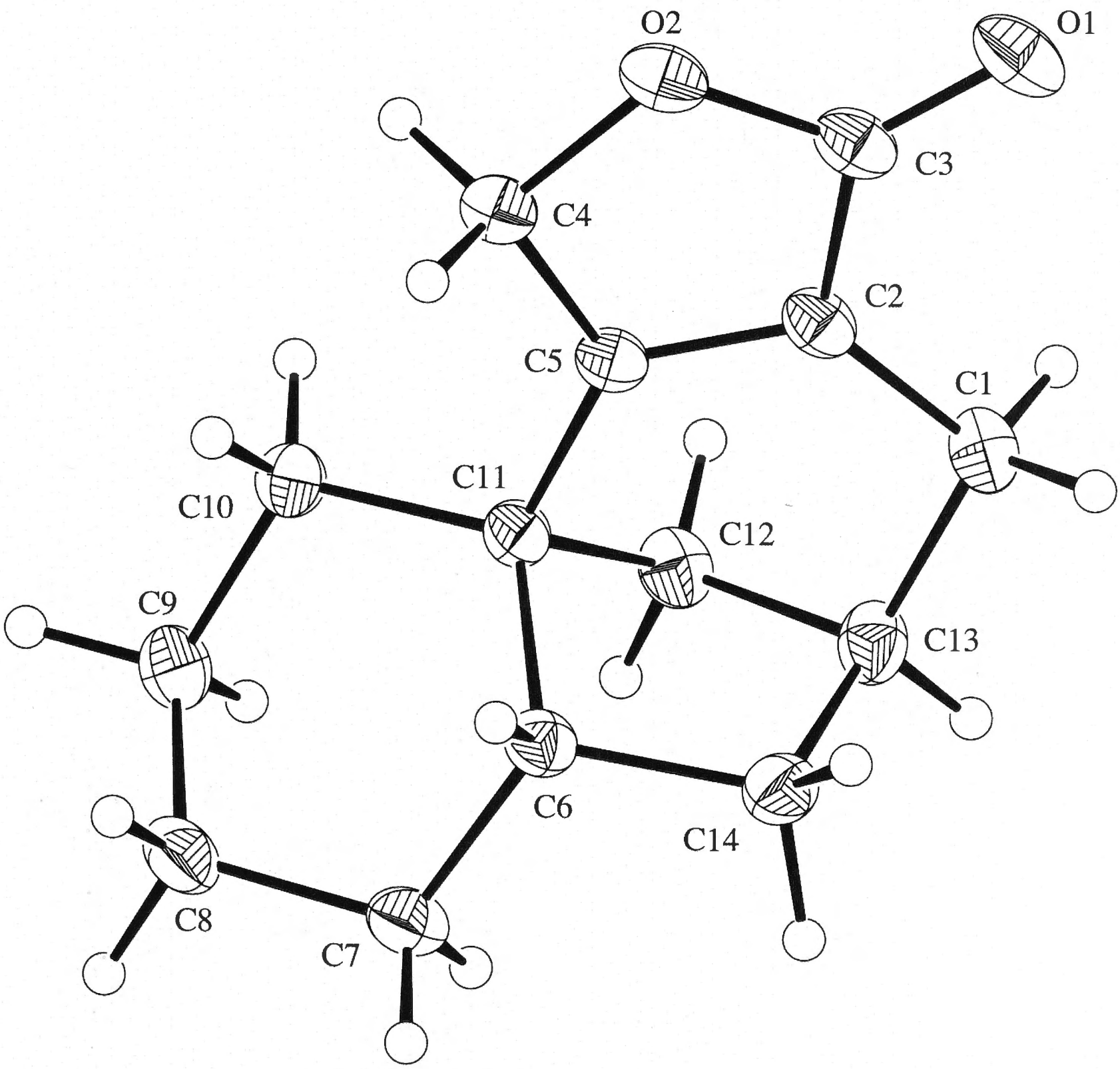
O1—C13—O2—C14	−1.3 (3)	C4—C5—C6—C7	−171.6 (2)
O1—C13—C2—C1	4.1 (3)	C4—C5—C6—C11	9.9 (2)
O1—C13—C2—C3	−173.6 (2)	C4—C12—C11—C6	−40.0 (2)
O2—C13—C2—C1	−175.8 (2)	C4—C12—C11—C10	−160.2 (1)
O2—C13—C2—C3	6.5 (3)	C5—C4—C12—C11	47.1 (2)
N1—C15—C1—C2	152 (10)	C5—C6—C7—C8	−175.9 (2)
N1—C15—C1—C11	28 (10)	C5—C6—C11—C10	144.2 (2)
C1—C2—C3—C4	−0.3 (3)	C5—C6—C11—C12	18.9 (2)
C1—C11—C6—C5	−94.7 (2)	C6—C5—C4—C12	−35.0 (2)
C1—C11—C6—C7	86.6 (2)	C6—C7—C8—C9	16.6 (3)
C1—C11—C10—C9	−71.4 (2)	C6—C11—C1—C15	−170.0 (1)
C1—C11—C12—C4	73.2 (2)	C6—C11—C10—C9	47.2 (2)
C2—C1—C11—C6	66.6 (2)	C7—C6—C11—C10	−34.4 (2)
C2—C1—C11—C10	−173.4 (2)	C7—C6—C11—C12	−159.8 (2)
C2—C1—C11—C12	−43.3 (2)	C7—C8—C9—C10	0.1 (3)
C2—C3—C4—C5	−78.0 (2)	C8—C7—C6—C11	2.5 (3)
C2—C3—C4—C12	32.8 (3)	C8—C9—C10—C11	−32.8 (3)
C2—C13—O2—C14	178.5 (2)	C9—C10—C11—C12	163.5 (2)
C3—C2—C1—C11	5.6 (3)	C10—C11—C1—C15	−49.9 (2)
C3—C2—C1—C15	−118.3 (2)	C11—C1—C2—C13	−172.1 (2)
C3—C4—C5—C6	80.0 (2)	C12—C11—C1—C15	80.2 (2)
C3—C4—C12—C11	−67.1 (2)	C13—C2—C1—C15	64.0 (2)
C4—C3—C2—C13	177.2 (2)		

Symmetry codes: (i) $x, -y+1, z-1/2$; (ii) $-x+3/2, y+1/2, -z+3/2$; (iii) $-x+1, -y+1, -z+1$; (iv) $-x+1, y, -z+3/2$; (v) $-x+1, -y, -z+1$; (vi) $x, y+1, z$.

Appendix 4

X-ray Crystal Structure Report for Compound 2.82.





Crystal structure of $C_{14}H_{18}O_2$ — ban1150

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Abstract

The crystal structure of $C_{14}H_{18}O_2$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{14}H_{18}O_2$.

Experimental

The compound was prepared by NH and crystallized from dimethylsulphoxide. The sample ID is NH8-FullyHd-tt5.

Refinement

Originally it was assumed that the crystal had an orthorhombic cell, but it was eventually recognized that the cell was actually monoclinic with a β angle very close to 90°. The structure was initially solved and refined assuming that there was no twinning and yielded an R-factor for all data, unit weights, of 0.24. A possible twin rule were identified using ROTAX within CRYSTALS (a rotation of 180° about reciprocal vector 1 0 0), and when this twinning was included in the refinement the R-factor lowered to 0.12 for the same stage of refinement. The final twin ratio was 0.70:0.30.

All H atoms were located in a subsequent difference electron density map and were included at calculated positions. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C—H in the range 0.93–0.98 Å) and with U_{iso}(H) in the range 1.2-1.5 times U_{eq} of the parent atom, after which the positions were refined with riding constraints and the displacement parameters were held fixed.

The largest peaks in the final difference electron density map are located midway along C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*-II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Acknowledgements

Thanks to Jas Ward for collecting the data set.

References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Mackay, S., Gilmore, C. J., Edwards, C., Stewart, N. & Shankland, K. (2000). *maXus* Computer Program for the Solution and Refinement of Crystal Structures. Nonius, The Netherlands, MacScience, Japan & The University of Glasgow.

Coppens, P. (1970). The Evaluation of Absorption and Extinction in Single-Crystal Structure Analysis. Crystallographic Computing. F. R. Ahmed, S. R. Hall and C. P. Huber, eds., Munksgaard. Copenhagen. pp 255-270.

Molecular Structure Corporation. (1992–1997). *TEXSAN*. Single Crystal Structure Analysis Software. Version 1.8. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Johnson, C. K. (1976). *ORTEP*II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.

(ban1150)

Crystal data

$C_{14}H_{18}O_2$
$M_r = 218.30$
Monoclinic, $P2_1/c$
$a = 6.6120\ (2)$ Å
$b = 11.4845\ (5)$ Å
$c = 14.9989\ (6)$ Å
$\beta = 90.017\ (2)°$
$V = 1138.95\ (8)$ Å^3
$Z = 4$
$F(000) = 472$
$D_x = 1.273$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 13249 reflections
$\theta = 2.6–27.5°$
$\mu = 0.08$ mm^{-1}
$T = 200$ K
Prism, Colourless
0.31 × 0.15 × 0.12 mm

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
φ and ω scans with CCD
Absorption correction: Integration via Gaussian method (Coppens, 1970) implemented in *maXus* (2000)

2206 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.042$
$\theta_{max} = 27.5°$, $\theta_{min} = 2.7°$
$h = -8 \rightarrow 7$

T_{min} = 0.981, T_{max} = 0.992
15817 measured reflections
2558 independent reflections

$k = -14 \rightarrow 14$
$l = -19 \rightarrow 19$

Refinement

Refinement on F^2

Least-squares matrix: Full

$R[F^2 > 2\sigma(F^2)] = 0.039$

$wR(F^2) = 0.102$

$S = 1.00$
2555 reflections
146 parameters
0 restraints

Primary atom site location: Structure-invariant direct methods
Hydrogen site location: Inferred from neighbouring sites
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.06P)^2 + 0.16P]$,
where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.0003$
$\Delta\rho_{max} = 0.16$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.28382 (18)	0.44245 (12)	0.39845 (7)	0.0497
O2	0.24319 (17)	0.58805 (10)	0.49750 (7)	0.0426
C1	0.2823 (3)	0.27527 (14)	0.56477 (10)	0.0421
C2	0.2559 (2)	0.40373 (13)	0.55711 (9)	0.0345
C3	0.2641 (2)	0.47296 (15)	0.47530 (10)	0.0382
C4	0.2196 (3)	0.59754 (13)	0.59316 (10)	0.0376
C5	0.2252 (2)	0.47481 (12)	0.62609 (9)	0.0313
C6	0.4247 (2)	0.41168 (14)	0.75655 (9)	0.0346
C7	0.4279 (3)	0.39477 (15)	0.85825 (10)	0.0423
C8	0.3098 (3)	0.48798 (15)	0.90812 (10)	0.0457
C9	0.0902 (3)	0.48970 (16)	0.87740 (11)	0.0457
C10	0.0796 (3)	0.51637 (15)	0.77753 (10)	0.0403
C11	0.2070 (2)	0.43281 (13)	0.72116 (9)	0.0323
C12	0.1257 (2)	0.30712 (15)	0.71409 (11)	0.0395
C13	0.2981 (3)	0.24611 (14)	0.66420 (10)	0.0413
C14	0.4904 (2)	0.30046 (15)	0.70607 (11)	0.0411
H11	0.4015	0.2504	0.5318	0.0500*
H12	0.1701	0.2340	0.5366	0.0503*
H41	0.3317	0.6439	0.6162	0.0440*
H42	0.0929	0.6367	0.6047	0.0450*
H61	0.5138	0.4789	0.7411	0.0393*
H71	0.5710	0.3966	0.8792	0.0507*
H72	0.3644	0.3168	0.8748	0.0508*
H81	0.3118	0.4713	0.9737	0.0540*
H82	0.3729	0.5650	0.8962	0.0539*
H91	0.0136	0.5507	0.9112	0.0550*
H92	0.0252	0.4129	0.8870	0.0545*
H101	0.1349	0.5967	0.7678	0.0473*
H102	−0.0631	0.5129	0.7565	0.0487*
H121	0.1055	0.2748	0.7746	0.0457*
H122	−0.0002	0.3014	0.6810	0.0460*
H131	0.2951	0.1622	0.6723	0.0491*
H141	0.5512	0.2435	0.7488	0.0495*
H142	0.5149	0.3197	0.6594	0.0480*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0455 (6)	0.0755 (8)	0.0282 (6)	−0.0113 (6)	−0.0002 (5)	0.0006 (5)
O2	0.0446 (6)	0.0499 (7)	0.0334 (5)	−0.0051 (5)	−0.0040 (5)	0.0104 (5)
C1	0.0494 (9)	0.0401 (8)	0.0368 (8)	−0.0058 (7)	0.0046 (7)	−0.0057 (6)

C2	0.0302 (7)	0.0431 (8)	0.0301 (7)	−0.0058 (6)	−0.0013 (6)	−0.0008 (6)
C3	0.0287 (7)	0.0527 (9)	0.0333 (7)	−0.0083 (6)	−0.0031 (6)	0.0018 (6)
C4	0.0386 (8)	0.0404 (8)	0.0338 (7)	−0.0018 (7)	−0.0026 (6)	0.0033 (6)
C5	0.0265 (6)	0.0356 (7)	0.0319 (7)	−0.0037 (6)	−0.0028 (6)	0.0018 (6)
C6	0.0348 (8)	0.0393 (8)	0.0296 (7)	0.0000 (6)	0.0013 (6)	0.0029 (6)
C7	0.0426 (9)	0.0523 (10)	0.0318 (8)	0.0008 (7)	−0.0038 (7)	0.0039 (7)
C8	0.0567 (11)	0.0510 (9)	0.0294 (7)	−0.0018 (8)	−0.0025 (7)	−0.0015 (7)
C9	0.0498 (10)	0.0530 (10)	0.0344 (8)	0.0037 (8)	0.0087 (7)	−0.0038 (7)
C10	0.0390 (8)	0.0455 (9)	0.0364 (8)	0.0069 (7)	0.0021 (7)	−0.0029 (7)
C11	0.0344 (7)	0.0342 (7)	0.0284 (7)	0.0001 (6)	0.0013 (6)	0.0007 (5)
C12	0.0433 (8)	0.0403 (8)	0.0350 (8)	−0.0058 (7)	0.0063 (7)	0.0013 (7)
C13	0.0528 (9)	0.0319 (7)	0.0393 (8)	−0.0008 (7)	0.0075 (7)	−0.0005 (6)
C14	0.0439 (9)	0.0442 (9)	0.0353 (8)	0.0086 (7)	0.0041 (7)	0.0046 (7)

Geometric parameters (Å, º)

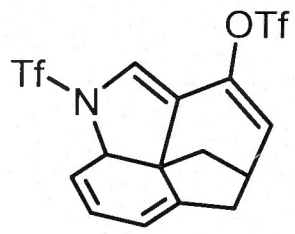
O1—C3	1.2118 (18)	C7—H72	1.020
O2—C3	1.370 (2)	C8—C9	1.523 (2)
O2—C4	1.4473 (17)	C8—H81	1.002
C1—C2	1.490 (2)	C8—H82	0.994
C1—C13	1.532 (2)	C9—C10	1.531 (2)
C1—H11	0.973	C9—H91	1.002
C1—H12	0.977	C9—H92	0.991
C2—C3	1.463 (2)	C10—C11	1.532 (2)
C2—C5	1.333 (2)	C10—H101	1.004
C4—C5	1.494 (2)	C10—H102	0.995
C4—H41	0.976	C11—C12	1.544 (2)
C4—H42	0.967	C12—C13	1.533 (2)
C5—C11	1.5101 (19)	C12—H121	0.989
C6—C7	1.538 (2)	C12—H122	0.971
C6—C11	1.553 (2)	C13—C14	1.549 (2)
C6—C14	1.547 (2)	C13—H131	0.971
C6—H61	0.999	C14—H141	1.000
C7—C8	1.521 (2)	C14—H142	1.008
C7—H71	0.997		
O1···C4^{i}	3.318 (2)	O2···C3^{i}	3.357 (2)
O1···C4^{ii}	3.362 (2)	O2···C2^{ii}	3.401 (2)
O1···C5^{i}	3.403 (2)	O2···C2^{i}	3.413 (2)
O1···C6^{i}	3.454 (2)	O2···C3^{ii}	3.451 (2)
O1···O2^{i}	3.512 (2)	C2···C3^{i}	3.509 (2)
O1···C5^{ii}	3.516 (2)	C3···C3^{i}	3.266 (3)
O1···C2^{i}	3.581 (2)	C3···C4^{ii}	3.455 (2)
C3—O2—C4	108.93 (11)	C9—C8—H82	109.5
C2—C1—C13	107.42 (12)	H81—C8—H82	110.0
C2—C1—H11	110.2	C8—C9—C10	110.00 (14)
C13—C1—H11	112.1	C8—C9—H91	109.8
C2—C1—H12	111.0	C10—C9—H91	109.3
C13—C1—H12	111.5	C8—C9—H92	111.0
H11—C1—H12	104.6	C10—C9—H92	107.5
C1—C2—C3	126.75 (13)	H91—C9—H92	109.2
C1—C2—C5	124.34 (13)	C9—C10—C11	112.94 (13)
C3—C2—C5	108.89 (13)	C9—C10—H101	108.1
C2—C3—O2	108.46 (12)	C11—C10—H101	107.2
C2—C3—O1	130.14 (16)	C9—C10—H102	110.2
O2—C3—O1	121.40 (14)	C11—C10—H102	108.7
O2—C4—C5	104.72 (12)	H101—C10—H102	109.6
O2—C4—H41	108.0	C10—C11—C6	114.78 (13)
C5—C4—H41	112.3	C10—C11—C5	111.41 (12)
O2—C4—H42	107.9	C6—C11—C5	107.38 (12)
C5—C4—H42	113.6	C10—C11—C12	115.58 (13)

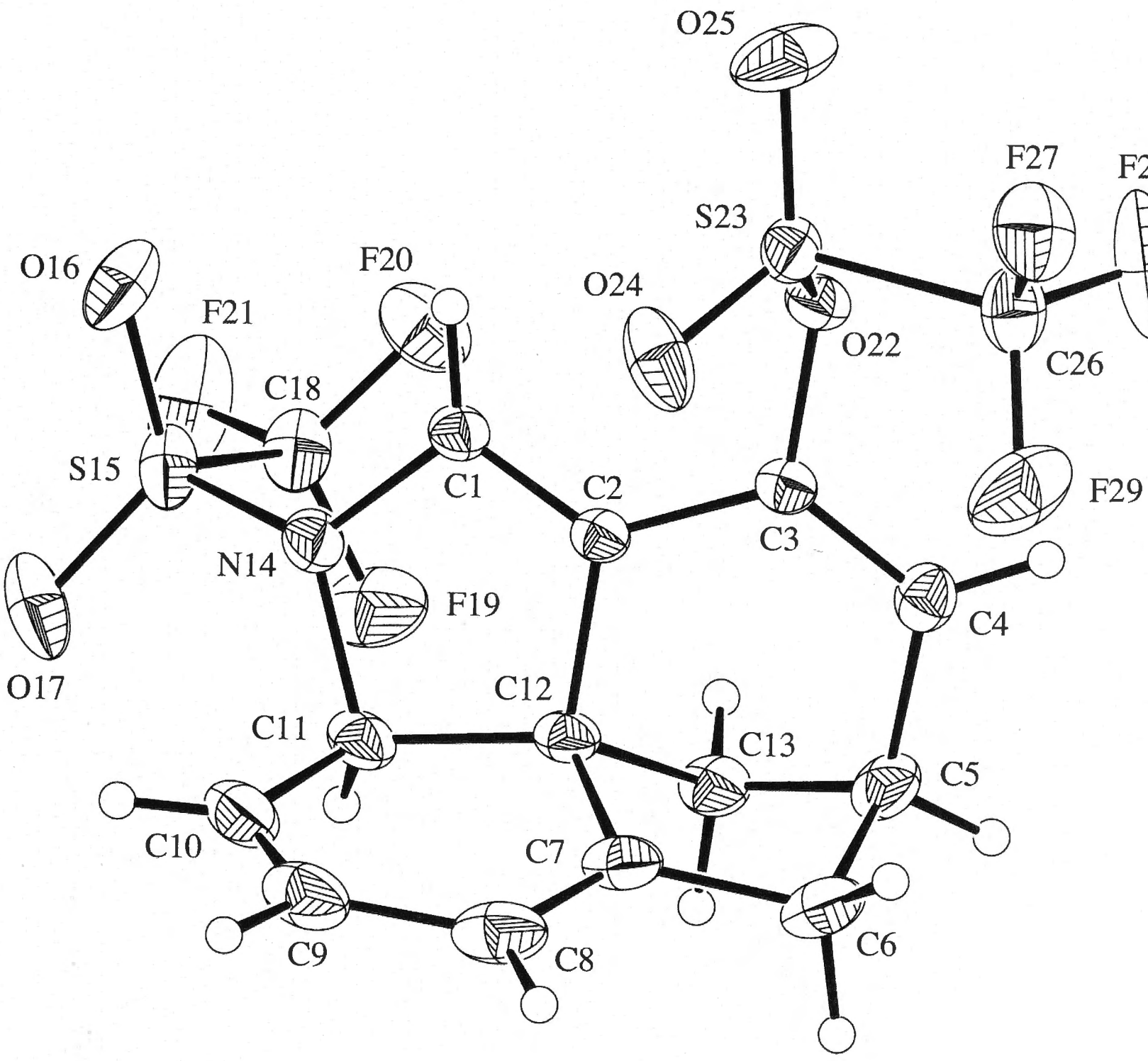
H41—C4—H42	109.9	C6—C11—C12	101.55 (12)
C4—C5—C2	108.95 (13)	C5—C11—C12	105.17 (12)
C4—C5—C11	127.70 (12)	C11—C12—C13	101.62 (12)
C2—C5—C11	123.32 (13)	C11—C12—H121	109.6
C7—C6—C11	111.79 (12)	C13—C12—H121	112.1
C7—C6—C14	112.17 (13)	C11—C12—H122	113.4
C11—C6—C14	102.84 (12)	C13—C12—H122	110.9
C7—C6—H61	108.6	H121—C12—H122	109.1
C11—C6—H61	110.3	C12—C13—C1	108.95 (14)
C14—C6—H61	111.0	C12—C13—C14	103.20 (12)
C6—C7—C8	113.08 (13)	C1—C13—C14	111.23 (13)
C6—C7—H71	108.8	C12—C13—H131	112.1
C8—C7—H71	108.5	C1—C13—H131	109.7
C6—C7—H72	110.3	C14—C13—H131	111.4
C8—C7—H72	106.7	C6—C14—C13	107.47 (12)
H71—C7—H72	109.4	C6—C14—H141	109.9
C7—C8—C9	110.46 (14)	C13—C14—H141	109.0
C7—C8—H81	110.0	C6—C14—H142	110.6
C9—C8—H81	108.2	C13—C14—H142	111.6
C7—C8—H82	108.8	H141—C14—H142	108.3
O1—C3—O2—C4	179.1 (1)	C4—C5—C11—C12	154.8 (1)
O1—C3—C2—C1	3.7 (3)	C5—C2—C1—C13	−8.0 (2)
O1—C3—C2—C5	−177.8 (1)	C5—C11—C6—C7	167.5 (1)
O2—C3—C2—C1	−176.8 (1)	C5—C11—C6—C14	−72.0 (1)
O2—C3—C2—C5	1.7 (2)	C5—C11—C10—C9	−169.2 (1)
O2—C4—C5—C2	2.0 (2)	C5—C11—C12—C13	63.1 (1)
O2—C4—C5—C11	−179.9 (1)	C6—C7—C8—C9	58.4 (2)
C1—C2—C5—C4	176.3 (2)	C6—C11—C10—C9	−46.9 (2)
C1—C2—C5—C11	−1.9 (2)	C6—C11—C12—C13	−48.6 (1)
C1—C13—C12—C11	−78.8 (2)	C6—C14—C13—C12	−15.8 (2)
C1—C13—C14—C6	100.9 (2)	C7—C6—C11—C10	43.0 (2)
C2—C1—C13—C12	48.4 (2)	C7—C6—C11—C12	−82.5 (1)
C2—C1—C13—C14	−64.7 (2)	C7—C6—C14—C13	106.4 (1)
C2—C3—O2—C4	−0.4 (2)	C7—C8—C9—C10	−60.3 (2)
C2—C5—C11—C6	80.2 (2)	C8—C7—C6—C11	−48.8 (2)
C2—C5—C11—C10	−153.3 (1)	C8—C7—C6—C14	−163.7 (1)
C2—C5—C11—C12	−27.4 (2)	C8—C9—C10—C11	54.8 (2)
C3—O2—C4—C5	−0.9 (2)	C9—C10—C11—C12	70.8 (2)
C3—C2—C1—C13	170.3 (1)	C10—C11—C6—C14	163.5 (1)
C3—C2—C5—C4	−2.3 (2)	C10—C11—C12—C13	−173.5 (1)
C3—C2—C5—C11	179.5 (1)	C11—C6—C14—C13	−13.9 (2)
C4—C5—C11—C6	−97.7 (2)	C11—C12—C13—C14	39.5 (1)
C4—C5—C11—C10	28.8 (2)	C12—C11—C6—C14	38.1 (1)

Symmetry codes: (i) $x+1, -y+1, -z+1$; (ii) $-x, -y+1, -z+1$.

Appendix 5

X-ray Crystal Structure Report for Compound 3.52.





Crystal structure of NH6-39 - cade029

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The crystal structure of NH6-39 is reported.

Experimental

Crystal data

$C_{15}H_{11}F_6NO_5S_2$
$M_r = 463.38$
Triclinic, $P\overline{1}$
$a = 6.8778$ (2) Å
$b = 10.8844$ (4) Å
$c = 12.8790$ (4) Å
$\alpha = 99.1558$ (19)°
$\beta = 102.708$ (2)°
$\gamma = 104.325$ (2)°
$V = 887.71$ (5) Å^3
$Z = 2$
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$\mu = 0.39$ mm^{-1}
$T = 200$ K
0.50 × 0.26 × 0.09 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: Integration Gaussian integration (Coppens, 1970)
$T_{min} = 0.898$, $T_{max} = 0.971$
18865 measured reflections
4063 independent reflections
3003 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.041$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.051$
$wR(F^2) = 0.132$
$S = 0.95$
4063 reflections
263 parameters
0 restraints
H-atom parameters constrained
$\Delta\rho_{max} = 0.88$ e Å^{-3}
$\Delta\rho_{min} = -0.54$ e Å^{-3}

Table 1

Selected geometric parameters (Å, °)

C1—C2	1.322 (3)	C11—N14	1.510 (3)
C1—N14	1.421 (3)	C12—C13	1.548 (3)
C2—C3	1.441 (3)	N14—S15	1.606 (2)
C2—C12	1.527 (3)	S15—O16	1.418 (2)
C3—C4	1.329 (3)	S15—O17	1.419 (2)
C3—O22	1.433 (3)	S15—C18	1.836 (3)
C4—C5	1.510 (4)	C18—F19	1.314 (3)
C5—C6	1.541 (4)	C18—F20	1.308 (3)
C5—C13	1.534 (4)	C18—F21	1.309 (4)
C6—C7	1.507 (4)	O22—S23	1.5648 (18)
C7—C8	1.333 (4)	S23—O24	1.401 (2)
C7—C12	1.524 (4)	S23—O25	1.408 (2)
C8—C9	1.450 (5)	S23—C26	1.825 (3)
C9—C10	1.314 (5)	C26—F27	1.308 (4)
C10—C11	1.508 (4)	C26—F28	1.294 (4)
C11—C12	1.543 (4)	C26—F29	1.331 (4)

C2—C1—N14	111.1 (2)	C11—N14—C1	108.9 (2)
C1—C2—C3	130.5 (2)	C11—N14—S15	123.48 (17)
C1—C2—C12	111.9 (2)	C1—N14—S15	123.03 (18)
C3—C2—C12	116.0 (2)	N14—S15—O16	109.33 (12)
C2—C3—C4	121.8 (2)	N14—S15—O17	107.98 (14)
C2—C3—O22	116.90 (19)	O16—S15—O17	123.01 (15)
C4—C3—O22	120.7 (2)	N14—S15—C18	105.01 (13)
C3—C4—C5	118.9 (2)	O16—S15—C18	104.67 (15)
C4—C5—C6	108.1 (2)	O17—S15—C18	105.36 (14)
C4—C5—C13	111.0 (2)	S15—C18—F19	110.5 (2)
C6—C5—C13	101.3 (2)	S15—C18—F20	110.1 (2)
C5—C6—C7	103.7 (2)	F19—C18—F20	107.9 (3)
C6—C7—C8	129.0 (3)	S15—C18—F21	111.0 (2)
C6—C7—C12	108.8 (2)	F19—C18—F21	109.0 (3)
C8—C7—C12	121.7 (3)	F20—C18—F21	108.2 (3)
C7—C8—C9	120.7 (3)	C3—O22—S23	119.42 (15)
C8—C9—C10	122.2 (3)	O22—S23—O24	111.92 (11)
C9—C10—C11	123.2 (3)	O22—S23—O25	105.79 (13)
C10—C11—C12	113.8 (3)	O24—S23—O25	122.33 (17)
C10—C11—N14	106.7 (2)	O22—S23—C26	101.47 (12)
C12—C11—N14	103.88 (19)	O24—S23—C26	107.80 (15)
C11—C12—C2	102.60 (19)	O25—S23—C26	105.41 (15)
C11—C12—C7	115.1 (2)	S23—C26—F27	109.7 (2)
C2—C12—C7	112.7 (2)	S23—C26—F28	111.0 (2)
C11—C12—C13	121.2 (2)	F27—C26—F28	110.8 (3)
C2—C12—C13	104.61 (19)	S23—C26—F29	108.6 (2)
C7—C12—C13	100.5 (2)	F27—C26—F29	108.5 (3)
C5—C13—C12	100.4 (2)	F28—C26—F29	108.1 (3)

Table 2

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C1—H11···O25^{i}	0.93	2.32	3.229 (4)	167 (1)

Symmetry code: (i) $-x+1, -y, -z$.

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP-3 for Windows* v. 2.01; software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Nonius (2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). Methods in Enzymology, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). J. Appl. Cryst. 36, 1487.

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). J. Appl. Cryst. 27, 435.

Larson, A. C. (1970). Crystallographic Computing, Ed Ahmed, F.R., Munksgaard, Copenhagen, 291-294.

Farrugia, L. J. (1997). *ORTEP-3 for Windows* v. 2.01, J. Appl. Cryst. 30, 565.

Coppens, P. (1970). In Crystallographic Computing, edited by F.R. Ahmed, S.R. Hall and C.P Huber, p255-270. Copenhagen: Munksgaard

supplementary materials

Crystal structure of NH6-39 - cade029

Martin G. Banwell,* Nora Heinrich and Ian A. Cade

Comment

The crystallographic asymmetric unit consists of one NH6-39 molecule.

Experimental

The title compound was recrystallised from dichloromethane

Refinement

In the absence of significant anomalous scattering, Friedel pairs were merged.

The absolute configuration was arbitrarily assigned.

The relatively large ratio of minimum to maximum corrections applied in the multiscan process (1:nnn) reflect changes in the illuminated volume of the crystal.

Changes in illuminated volume were kept to a minimum, and were taken into account (Görbitz, 1999) by the multi-scan inter-frame scaling (DENZO/SCALEPACK, Otwinowski & Minor, 1997).

Görbitz, C. H. (1999). Acta Cryst. B55, 1090-1098.

The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C—H in the range 0.93–0.98, N—H in the range 0.86–0.89 N—H to 0.86 O—H = 0.82 Å) and U_{iso}(H) (in the range 1.2-1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints (Cooper *et al.*, 2010).

Cooper, R. I., Thompson, A. L. & Watkin, D. J. (2010). J. Appl. Cryst. 43, 1100-1107.

(1)

Crystal data

$C_{15}H_{11}F_6NO_5S_2$	$Z = 2$
$M_r = 463.38$	$F(000) = 468$
Triclinic, $P\overline{1}$	$D_x = 1.733$ Mg m^{-3}
$a = 6.8778$ (2) Å	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$b = 10.8844$ (4) Å	Cell parameters from 10969 reflections
$c = 12.8790$ (4) Å	$\theta = 2.6$–$27.5°$
$\alpha = 99.1558$ (19)°	$\mu = 0.39$ mm^{-1}
$\beta = 102.708$ (2)°	$T = 200$ K
$\gamma = 104.325$ (2)°	Plate, Colourless
$V = 887.71$ (5) Å^3	0.50 × 0.26 × 0.09 mm

Data collection

Nonius KappaCCD diffractometer	3003 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.041$
ω scans	$\theta_{max} = 27.6°$, $\theta_{min} = 2.9°$
Absorption correction: Integration Gaussian integration (Coppens, 1970)	$h = -8 \rightarrow 8$
$T_{min} = 0.898$, $T_{max} = 0.971$	$k = -14 \rightarrow 14$
18865 measured reflections	$l = -16 \rightarrow 16$
4063 independent reflections	

Refinement

Refinement on F^2
Least-squares matrix: Full

$R[F^2 > 2\sigma(F^2)] = 0.051$

$wR(F^2) = 0.132$
$S = 0.95$
4063 reflections
263 parameters
0 restraints
Primary atom site location: Direct

Hydrogen site location: Difference Fourier map
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.06P)^2 + 1.01P]$,
where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.88$ e Å^{-3}
$\Delta\rho_{min} = -0.54$ e Å^{-3}
Extinction correction: Larson (1970), Equation 22
Extinction coefficient: 150 (20)

Special details

Experimental. The crystal was placed in the cold stream of an Oxford Cryosystems open-flow nitrogen cryostat (Cosier & Glazer, 1986) with a nominal stability of 0.1K.

Cosier, J. & Glazer, A.M., 1986. J. Appl. Cryst. 105-107.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.4963 (4)	0.2519 (2)	0.2134 (2)	0.0333
C2	0.3374 (3)	0.1817 (2)	0.24101 (18)	0.0299
C3	0.1650 (4)	0.0714 (2)	0.17725 (19)	0.0322
C4	−0.0208 (4)	0.0481 (3)	0.1970 (2)	0.0396
C5	−0.0468 (4)	0.1335 (3)	0.2944 (2)	0.0459
C6	0.0460 (5)	0.0904 (3)	0.3978 (2)	0.0547
C7	0.2759 (4)	0.1595 (3)	0.4254 (2)	0.0454
C8	0.4290 (5)	0.1596 (4)	0.5094 (2)	0.0591
C9	0.6358 (5)	0.2497 (4)	0.5325 (2)	0.0611
C10	0.6747 (5)	0.3452 (4)	0.4822 (2)	0.0563
C11	0.5138 (4)	0.3651 (3)	0.3912 (2)	0.0421
C12	0.3121 (4)	0.2501 (3)	0.34815 (19)	0.0352
C13	0.0957 (4)	0.2731 (3)	0.3164 (2)	0.0425
N14	0.6045 (3)	0.3680 (2)	0.29472 (18)	0.0401
S15	0.72678 (10)	0.49990 (6)	0.26774 (7)	0.0479
O16	0.8343 (3)	0.4693 (2)	0.1897 (2)	0.0610
O17	0.8249 (3)	0.5934 (2)	0.3679 (2)	0.0688
C18	0.5218 (5)	0.5603 (3)	0.1950 (3)	0.0506
F19	0.3893 (3)	0.5717 (2)	0.25280 (17)	0.0802
F20	0.4182 (3)	0.4787 (2)	0.10170 (16)	0.0721
F21	0.6015 (3)	0.6735 (2)	0.1749 (3)	0.0959
O22	0.1930 (3)	−0.00146 (16)	0.08153 (13)	0.0368
S23	0.30209 (10)	−0.11083 (6)	0.09238 (6)	0.0407
O24	0.4459 (3)	−0.0845 (2)	0.1946 (2)	0.0665
O25	0.3557 (5)	−0.1394 (2)	−0.0063 (2)	0.0782
C26	0.0831 (5)	−0.2494 (3)	0.0859 (3)	0.0518
F27	0.1326 (3)	−0.35740 (17)	0.06454 (18)	0.0695
F28	−0.0825 (3)	−0.2520 (2)	0.0136 (2)	0.1055
F29	0.0426 (4)	−0.2376 (2)	0.1829 (2)	0.0883
H11	0.5375	0.2325	0.1505	0.0402*
H41	−0.1326	−0.0217	0.1519	0.0479*
H51	−0.1913	0.1302	0.2862	0.0544*
H62	−0.0084	0.1203	0.4566	0.0660*

H61	0.0163	−0.0025	0.3849	0.0657*
H81	0.4018	0.1015	0.5526	0.0711*
H91	0.7447	0.2416	0.5870	0.0731*
H101	0.8071	0.4034	0.5033	0.0680*
H111	0.4818	0.4469	0.4120	0.0510*
H131	0.0699	0.3277	0.3764	0.0511*
H132	0.0767	0.3108	0.2533	0.0508*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0349 (12)	0.0322 (12)	0.0327 (12)	0.0125 (10)	0.0103 (10)	0.0015 (9)
C2	0.0301 (11)	0.0341 (12)	0.0278 (11)	0.0153 (9)	0.0072 (9)	0.0050 (9)
C3	0.0350 (12)	0.0348 (12)	0.0282 (12)	0.0133 (10)	0.0081 (9)	0.0068 (9)
C4	0.0327 (13)	0.0444 (14)	0.0428 (14)	0.0127 (11)	0.0079 (11)	0.0135 (11)
C5	0.0333 (13)	0.0621 (18)	0.0510 (16)	0.0213 (12)	0.0185 (12)	0.0155 (13)
C6	0.0562 (18)	0.076 (2)	0.0487 (17)	0.0269 (16)	0.0308 (15)	0.0251 (16)
C7	0.0513 (16)	0.0628 (18)	0.0340 (14)	0.0304 (14)	0.0191 (12)	0.0127 (12)
C8	0.072 (2)	0.086 (2)	0.0382 (15)	0.0441 (19)	0.0218 (15)	0.0247 (16)
C9	0.0573 (19)	0.094 (3)	0.0343 (15)	0.0412 (19)	0.0021 (13)	0.0066 (16)
C10	0.0461 (16)	0.078 (2)	0.0364 (15)	0.0247 (15)	0.0012 (12)	−0.0075 (15)
C11	0.0420 (14)	0.0460 (15)	0.0354 (13)	0.0192 (12)	0.0083 (11)	−0.0059 (11)
C12	0.0361 (13)	0.0459 (14)	0.0276 (12)	0.0206 (11)	0.0099 (10)	0.0041 (10)
C13	0.0395 (14)	0.0536 (16)	0.0407 (14)	0.0259 (12)	0.0132 (11)	0.0061 (12)
N14	0.0385 (11)	0.0348 (11)	0.0419 (12)	0.0088 (9)	0.0110 (9)	−0.0025 (9)
S15	0.0326 (3)	0.0341 (4)	0.0694 (5)	0.0079 (3)	0.0069 (3)	0.0034 (3)
O16	0.0457 (11)	0.0499 (12)	0.1023 (18)	0.0181 (9)	0.0399 (12)	0.0248 (12)
O17	0.0521 (13)	0.0407 (12)	0.0851 (17)	0.0065 (10)	−0.0136 (12)	−0.0097 (11)
C18	0.0427 (15)	0.0403 (15)	0.068 (2)	0.0142 (12)	0.0131 (14)	0.0085 (14)
F19	0.0728 (13)	0.1234 (19)	0.0711 (13)	0.0662 (14)	0.0279 (11)	0.0264 (13)
F20	0.0807 (14)	0.0710 (13)	0.0570 (12)	0.0304 (11)	−0.0001 (10)	0.0067 (10)
F21	0.0639 (13)	0.0535 (12)	0.174 (3)	0.0204 (10)	0.0188 (14)	0.0493 (14)
O22	0.0437 (10)	0.0339 (9)	0.0311 (9)	0.0107 (7)	0.0111 (7)	0.0028 (7)
S23	0.0373 (3)	0.0314 (3)	0.0498 (4)	0.0066 (2)	0.0156 (3)	−0.0008 (3)
O24	0.0474 (12)	0.0513 (13)	0.0806 (16)	0.0232 (10)	−0.0160 (11)	−0.0087 (11)
O25	0.117 (2)	0.0442 (12)	0.0954 (19)	0.0227 (13)	0.0791 (18)	0.0088 (12)
C26	0.0458 (16)	0.0392 (15)	0.0632 (19)	0.0042 (12)	0.0064 (14)	0.0163 (14)
F27	0.0763 (13)	0.0337 (9)	0.0905 (14)	0.0097 (8)	0.0171 (11)	0.0092 (9)
F28	0.0582 (13)	0.0632 (13)	0.147 (2)	−0.0144 (10)	−0.0389 (14)	0.0328 (14)
F29	0.1052 (18)	0.0673 (14)	0.1134 (19)	0.0172 (12)	0.0695 (15)	0.0372 (13)

Geometric parameters (Å, º)

C1—C2	1.322 (3)	C10—H101	0.925
C1—N14	1.421 (3)	C11—C12	1.543 (4)
C1—H11	0.927	C11—N14	1.510 (3)
C2—C3	1.441 (3)	C11—H111	0.979
C2—C12	1.527 (3)	C12—C13	1.548 (3)
C3—C4	1.329 (3)	C13—H131	0.973
C3—O22	1.433 (3)	C13—H132	0.965
C4—C5	1.510 (4)	N14—S15	1.606 (2)
C4—H41	0.938	S15—O16	1.418 (2)
C5—C6	1.541 (4)	S15—O17	1.419 (2)
C5—C13	1.534 (4)	S15—C18	1.836 (3)
C5—H51	0.967	C18—F19	1.314 (3)
C6—C7	1.507 (4)	C18—F20	1.308 (3)

C6—H62	0.962	C18—F21	1.309 (4)
C6—H61	0.959	O22—S23	1.5648 (18)
C7—C8	1.333 (4)	S23—O24	1.401 (2)
C7—C12	1.524 (4)	S23—O25	1.408 (2)
C8—C9	1.450 (5)	S23—C26	1.825 (3)
C8—H81	0.919	C26—F27	1.308 (4)
C9—C10	1.314 (5)	C26—F28	1.294 (4)
C9—H91	0.940	C26—F29	1.331 (4)
C10—C11	1.508 (4)		

C2—C1—N14	111.1 (2)	N14—C11—H111	109.7
C2—C1—H11	127.4	C11—C12—C2	102.60 (19)
N14—C1—H11	121.5	C11—C12—C7	115.1 (2)
C1—C2—C3	130.5 (2)	C2—C12—C7	112.7 (2)
C1—C2—C12	111.9 (2)	C11—C12—C13	121.2 (2)
C3—C2—C12	116.0 (2)	C2—C12—C13	104.61 (19)
C2—C3—C4	121.8 (2)	C7—C12—C13	100.5 (2)
C2—C3—O22	116.90 (19)	C5—C13—C12	100.4 (2)
C4—C3—O22	120.7 (2)	C5—C13—H131	109.6
C3—C4—C5	118.9 (2)	C12—C13—H131	112.3
C3—C4—H41	120.1	C5—C13—H132	112.9
C5—C4—H41	120.9	C12—C13—H132	112.4
C4—C5—C6	108.1 (2)	H131—C13—H132	109.0
C4—C5—C13	111.0 (2)	C11—N14—C1	108.9 (2)
C6—C5—C13	101.3 (2)	C11—N14—S15	123.48 (17)
C4—C5—H51	111.3	C1—N14—S15	123.03 (18)
C6—C5—H51	112.2	N14—S15—O16	109.33 (12)
C13—C5—H51	112.4	N14—S15—O17	107.98 (14)
C5—C6—C7	103.7 (2)	O16—S15—O17	123.01 (15)
C5—C6—H62	110.2	N14—S15—C18	105.01 (13)
C7—C6—H62	109.3	O16—S15—C18	104.67 (15)
C5—C6—H61	111.6	O17—S15—C18	105.36 (14)
C7—C6—H61	112.7	S15—C18—F19	110.5 (2)
H62—C6—H61	109.3	S15—C18—F20	110.1 (2)
C6—C7—C8	129.0 (3)	F19—C18—F20	107.9 (3)
C6—C7—C12	108.8 (2)	S15—C18—F21	111.0 (2)
C8—C7—C12	121.7 (3)	F19—C18—F21	109.0 (3)
C7—C8—C9	120.7 (3)	F20—C18—F21	108.2 (3)
C7—C8—H81	119.0	C3—O22—S23	119.42 (15)
C9—C8—H81	120.3	O22—S23—O24	111.92 (11)
C8—C9—C10	122.2 (3)	O22—S23—O25	105.79 (13)
C8—C9—H91	119.1	O24—S23—O25	122.33 (17)
C10—C9—H91	118.7	O22—S23—C26	101.47 (12)
C9—C10—C11	123.2 (3)	O24—S23—C26	107.80 (15)
C9—C10—H101	118.8	O25—S23—C26	105.41 (15)
C11—C10—H101	118.0	S23—C26—F27	109.7 (2)
C10—C11—C12	113.8 (3)	S23—C26—F28	111.0 (2)
C10—C11—N14	106.7 (2)	F27—C26—F28	110.8 (3)
C12—C11—N14	103.88 (19)	S23—C26—F29	108.6 (2)
C10—C11—H111	111.6	F27—C26—F29	108.5 (3)
C12—C11—H111	110.7	F28—C26—F29	108.1 (3)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*

C1—H11···O25^{i}	0.93	2.32	3.229 (4)	167 (1)

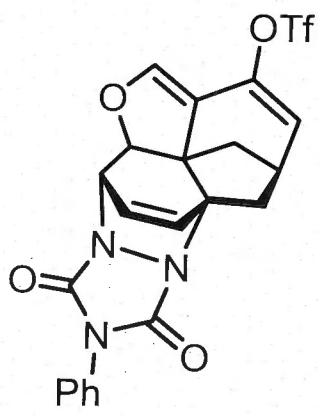
Symmetry code: (i) $-x+1, -y, -z$.

Figure 1

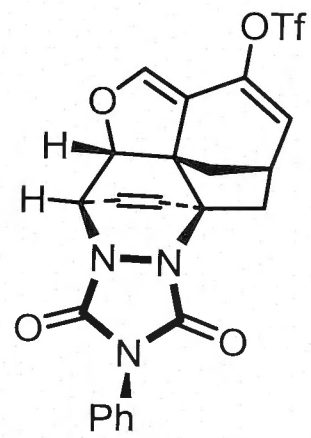
Fig. 1. The title compound with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitary radius.

Appendix 6

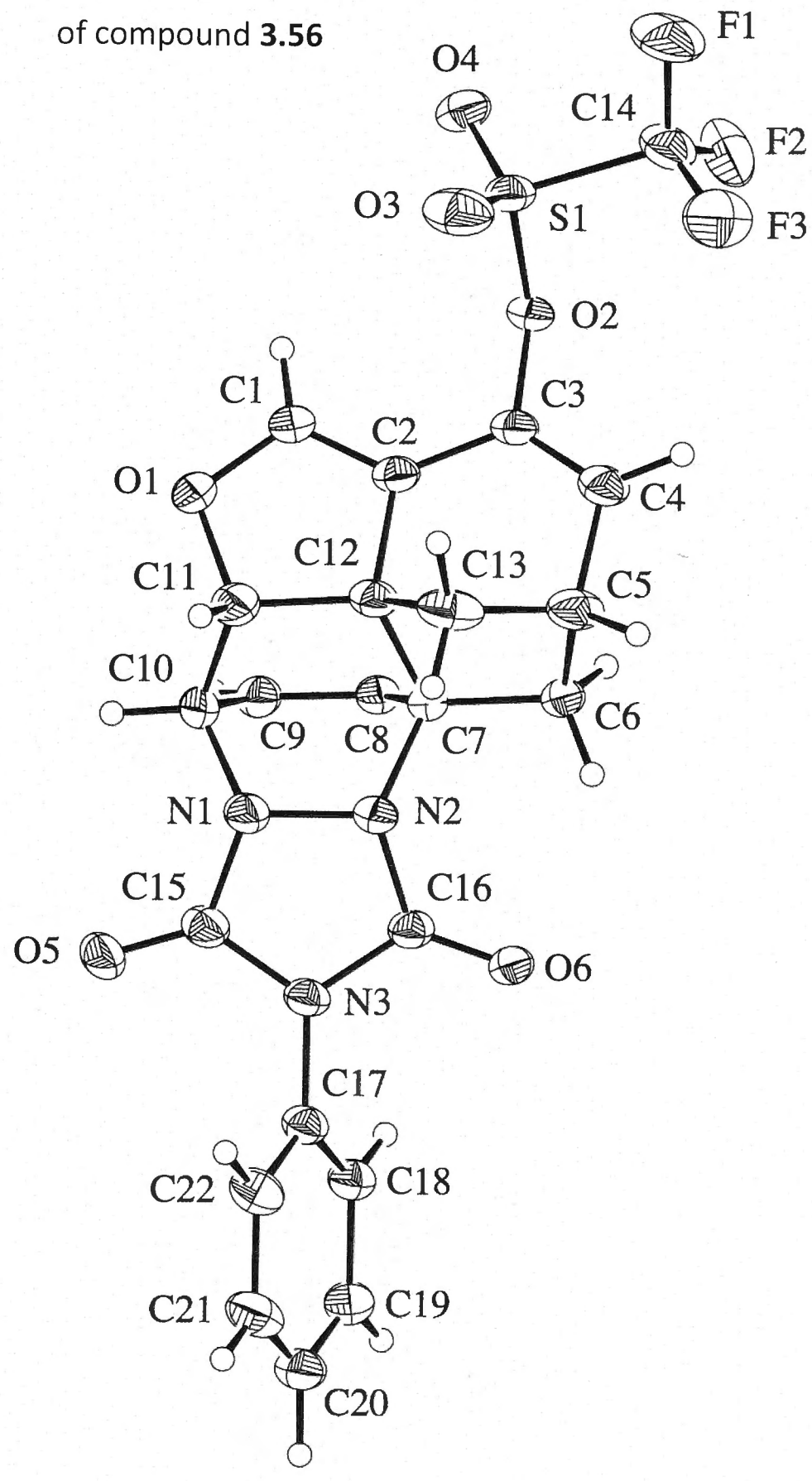
X-ray Crystal Structure Report for Compound 3.56.



3.56



Enantiomeric form of compound **3.56**



Crystal structure of $C_{22}H_{16}F_3N_3O_6S$ — ban1211

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Abstract

The crystal structure of $C_{22}H_{16}F_3N_3O_6S$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{22}H_{16}F_3N_3O_6S$. There is some disorder in the packing of the triflate group.

Experimental

The compound was prepared by NH and crystallized from pentane/ether. The sample ID is NH9-71-f1.

Refinement

After location of the major sites for all atoms, a difference electron-density map showed a significant peak attributable to an alternative location of the S atom of the triflate group. This suggested that the triflate group could pack in two orientations within the unit cell. Alternative sites were then located for the other atoms of the group. Isotropic displacement parameters were used for these minor sites. Restraints were applied to distances, angles and some displacement parameters (U[iso] of O103 and O104 to be similar; U[iso] of F101, F102 and F103 to be similar) for this minor image of the group. Relative occupancies of atom sites were refined appropriately.

All H atoms were located in a difference electron-density map and were included at calculated positions. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C—H in the range 0.93–0.98 Å) and with U_{iso}(H) in the range 1.2-1.5 times U_{eq} of the parent atom, after which the positions were refined with riding restraints and the displacement parameters were held fixed.

Most of the largest peaks in the final difference electron density map are located in the disorder or midway along C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*-II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Mackay, S., Gilmore, C. J., Edwards, C., Stewart, N. & Shankland, K. (2000). *maXus* Computer Program for the Solution and Refinement of Crystal Structures. Nonius, The Netherlands, MacScience, Japan & The University of Glasgow.

Coppens, P. (1970). The Evaluation of Absorption and Extinction in Single-Crystal Structure Analysis. Crystallographic Computing. F. R. Ahmed, S. R. Hall and C. P. Huber, eds., Munksgaard. Copenhagen. pp 255-270.

Molecular Structure Corporation. (1992–1997). *TEXSAN*. Single Crystal Structure Analysis Software. Version 1.8. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Johnson, C. K. (1976). *ORTEP*II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.

(ban1211)

Crystal data

$C_{22}H_{16}F_3N_3O_6S$
$M_r = 507.45$
Triclinic, $P\overline{1}$
$a = 6.6517\ (2)$ Å
$b = 11.4024\ (6)$ Å
$c = 14.7561\ (8)$ Å
$\alpha = 79.894\ (2)°$
$\beta = 83.096\ (3)°$
$\gamma = 78.323\ (3)°$
$V = 1074.84\ (9)$ Å^3
$Z = 2$
$F(000) = 520$
$D_x = 1.568$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 17589 reflections
$\theta = 3–27°$
$\mu = 0.22$ mm^{-1}
$T = 200$ K
Needle, Colourless
$0.42 \times 0.06 \times 0.04$ mm

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
φ and ω scans with CCD
Absorption correction: Integration via Gaussian method (Coppens, 1970) implemented in *maXus* (2000)
$T_{min} = 0.948$, $T_{max} = 0.992$
22295 measured reflections
4921 independent reflections
3027 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.061$
$\theta_{max} = 27.5°$, $\theta_{min} = 2.8°$
$h = -8 \rightarrow 7$
$k = -14 \rightarrow 14$
$l = -19 \rightarrow 19$

Refinement

Refinement on F^2
Least-squares matrix: Full
$R[F^2 > 2\sigma(F^2)] = 0.060$
$wR(F^2) = 0.153$
$S = 0.97$
4921 reflections
349 parameters
23 restraints
Primary atom site location: Structure-invariant direct methods
Hydrogen site location: Inferred from neighbouring sites
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.06P)^2 + 0.86P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.002$
$\Delta\rho_{max} = 0.50$ e Å^{-3}
$\Delta\rho_{min} = -0.62$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
S1	0.32886 (13)	0.33022 (8)	0.98819 (6)	0.0480	0.879 (3)
S101	0.4606 (18)	0.2450 (12)	0.9774 (9)	0.106 (4)*	0.121 (3)
F1	0.3889 (5)	0.1188 (2)	1.0873 (2)	0.1032	0.879 (3)
F2	0.6468 (5)	0.2087 (2)	1.07279 (19)	0.0889	0.879 (3)
F3	0.5805 (5)	0.1313 (2)	0.9599 (2)	0.0966	0.879 (3)
F101	0.139 (6)	0.324 (4)	0.886 (2)	0.206 (17)*	0.121 (3)
F102	0.128 (5)	0.387 (3)	1.017 (3)	0.194 (14)*	0.121 (3)
F103	0.106 (6)	0.201 (3)	1.013 (3)	0.227 (14)*	0.121 (3)
O1	0.1330 (3)	0.6837 (2)	0.75675 (15)	0.0656	
O2	0.4924 (5)	0.4051 (4)	0.93754 (16)	0.0425	0.879 (3)
O3	0.2050 (5)	0.3053 (3)	0.9267 (3)	0.0785	0.879 (3)
O4	0.2445 (4)	0.3816 (2)	1.06795 (18)	0.0622	0.879 (3)
O5	0.3761 (3)	0.9355 (2)	0.44161 (16)	0.0641	
O6	0.9684 (3)	0.65905 (17)	0.49439 (14)	0.0520	
O102	0.517 (6)	0.372 (2)	0.9343 (14)	0.105 (19)*	0.121 (3)
O103	0.505 (6)	0.166 (3)	0.910 (2)	0.180 (19)*	0.121 (3)
O104	0.507 (7)	0.211 (4)	1.0699 (19)	0.20 (2)*	0.121 (3)
N1	0.4431 (3)	0.7531 (2)	0.54003 (16)	0.0482	
N2	0.6269 (3)	0.6639 (2)	0.55645 (15)	0.0430	
N3	0.6935 (3)	0.8038 (2)	0.43858 (15)	0.0426	
C1	0.2292 (4)	0.6014 (3)	0.8232 (2)	0.0544	
C2	0.4003 (4)	0.5313 (3)	0.79362 (18)	0.0415	
C3	0.5269 (4)	0.4254 (3)	0.83789 (18)	0.0431	
C4	0.6703 (5)	0.3560 (3)	0.7929 (2)	0.0591	
C5	0.6986 (6)	0.3932 (3)	0.6884 (2)	0.0625	
C6	0.8136 (4)	0.5020 (2)	0.6688 (2)	0.0497	
C7	0.6419 (4)	0.6148 (2)	0.65708 (18)	0.0374	
C8	0.6370 (4)	0.7233 (2)	0.70304 (18)	0.0400	
C9	0.4722 (4)	0.8096 (3)	0.6870 (2)	0.0469	
C10	0.3274 (4)	0.7822 (3)	0.6264 (2)	0.0522	
C11	0.2494 (4)	0.6665 (3)	0.6689 (2)	0.0548	
C12	0.4367 (4)	0.5640 (3)	0.68935 (19)	0.0432	
C13	0.4891 (6)	0.4453 (3)	0.6496 (2)	0.0618	
C14	0.5004 (8)	0.1876 (4)	1.0312 (3)	0.0652	0.879 (3)
C15	0.4908 (4)	0.8436 (3)	0.4700 (2)	0.0482	
C16	0.7872 (4)	0.7039 (2)	0.49784 (19)	0.0414	
C17	0.7979 (4)	0.8617 (2)	0.35768 (19)	0.0427	
C18	0.9658 (4)	0.9121 (3)	0.3655 (2)	0.0475	
C19	1.0653 (5)	0.9676 (3)	0.2863 (2)	0.0580	
C20	0.9967 (5)	0.9729 (3)	0.2015 (2)	0.0627	
C21	0.8301 (6)	0.9218 (3)	0.1939 (2)	0.0634	
C22	0.7289 (5)	0.8653 (3)	0.2720 (2)	0.0536	
C114	0.185 (3)	0.294 (3)	0.972 (2)	0.12 (2)*	0.121 (3)
H11	0.1735	0.5983	0.8837	0.0650*	
H41	0.7540	0.2868	0.8228	0.0708*	
H51	0.7735	0.3250	0.6591	0.0747*	
H61	0.8908	0.5029	0.7224	0.0599*	
H62	0.9026	0.4981	0.6137	0.0591*	
H81	0.7464	0.7293	0.7379	0.0486*	
H91	0.4460	0.8831	0.7118	0.0567*	
H101	0.2106	0.8484	0.6127	0.0630*	
H111	0.1624	0.6466	0.6263	0.0668*	

H131	0.3855	0.3927	0.6702	0.0733*
H132	0.5039	0.4657	0.5820	0.0734*
H181	1.0127	0.9080	0.4231	0.0563*
H191	1.1802	1.0017	0.2921	0.0699*
H201	1.0671	1.0110	0.1466	0.0750*
H211	0.7833	0.9236	0.1360	0.0763*
H221	0.6151	0.8314	0.2687	0.0639*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0465 (5)	0.0539 (6)	0.0415 (5)	−0.0183 (4)	0.0053 (4)	0.0023 (4)
F1	0.136 (2)	0.0588 (15)	0.100 (2)	−0.0343 (15)	0.0246 (17)	0.0231 (14)
F2	0.090 (2)	0.0703 (16)	0.098 (2)	−0.0012 (14)	−0.0338 (16)	0.0100 (14)
F3	0.138 (3)	0.0499 (14)	0.090 (2)	−0.0072 (15)	0.0299 (19)	−0.0185 (14)
O1	0.0342 (11)	0.0809 (16)	0.0636 (14)	−0.0031 (10)	0.0083 (10)	0.0199 (12)
O2	0.0471 (15)	0.0415 (15)	0.0363 (15)	−0.0147 (13)	0.0030 (9)	0.0039 (10)
O3	0.081 (2)	0.099 (2)	0.064 (2)	−0.0529 (19)	−0.0061 (16)	0.0074 (17)
O4	0.0609 (16)	0.0674 (17)	0.0510 (15)	−0.0103 (12)	0.0182 (12)	−0.0066 (12)
O5	0.0409 (11)	0.0734 (16)	0.0666 (15)	−0.0101 (11)	−0.0132 (10)	0.0253 (12)
O6	0.0516 (13)	0.0430 (11)	0.0496 (12)	−0.0005 (9)	0.0157 (9)	0.0014 (9)
N1	0.0384 (13)	0.0537 (15)	0.0482 (14)	−0.0139 (11)	−0.0032 (10)	0.0091 (12)
N2	0.0449 (13)	0.0390 (13)	0.0410 (13)	−0.0100 (10)	0.0032 (10)	0.0025 (10)
N3	0.0447 (13)	0.0413 (13)	0.0397 (13)	−0.0143 (10)	−0.0007 (10)	0.0043 (10)
C1	0.0417 (16)	0.0586 (19)	0.0519 (18)	−0.0087 (14)	0.0093 (13)	0.0111 (15)
C2	0.0397 (15)	0.0485 (16)	0.0364 (15)	−0.0167 (12)	0.0028 (11)	−0.0013 (12)
C3	0.0465 (16)	0.0448 (16)	0.0355 (15)	−0.0144 (13)	0.0051 (12)	0.0019 (12)
C4	0.072 (2)	0.0361 (16)	0.057 (2)	−0.0058 (14)	0.0155 (16)	0.0072 (14)
C5	0.090 (2)	0.0331 (16)	0.0542 (19)	−0.0088 (15)	0.0255 (17)	−0.0044 (14)
C6	0.0504 (17)	0.0388 (15)	0.0487 (17)	−0.0002 (12)	0.0147 (13)	0.0015 (13)
C7	0.0354 (13)	0.0378 (14)	0.0347 (14)	−0.0057 (11)	0.0031 (10)	0.0004 (11)
C8	0.0376 (14)	0.0406 (15)	0.0404 (15)	−0.0116 (11)	0.0006 (11)	−0.0004 (12)
C9	0.0483 (16)	0.0390 (15)	0.0480 (17)	−0.0059 (12)	0.0074 (13)	−0.0026 (13)
C10	0.0336 (14)	0.0586 (19)	0.0525 (18)	−0.0015 (13)	−0.0013 (12)	0.0137 (14)
C11	0.0363 (15)	0.069 (2)	0.0560 (19)	−0.0178 (14)	−0.0037 (13)	0.0088 (16)
C12	0.0450 (15)	0.0454 (16)	0.0398 (15)	−0.0193 (12)	−0.0008 (12)	0.0029 (12)
C13	0.096 (3)	0.0532 (19)	0.0426 (18)	−0.0377 (18)	0.0082 (17)	−0.0068 (15)
C14	0.086 (3)	0.043 (2)	0.059 (3)	−0.014 (2)	0.004 (2)	0.009 (2)
C15	0.0411 (16)	0.0564 (19)	0.0469 (17)	−0.0196 (14)	−0.0092 (13)	0.0081 (14)
C16	0.0472 (16)	0.0351 (14)	0.0406 (16)	−0.0114 (12)	0.0064 (12)	−0.0049 (12)
C17	0.0506 (16)	0.0347 (14)	0.0404 (16)	−0.0105 (12)	0.0017 (12)	0.0002 (12)
C18	0.0478 (16)	0.0476 (17)	0.0449 (17)	−0.0135 (13)	−0.0008 (12)	0.0018 (13)
C19	0.0482 (17)	0.0553 (19)	0.064 (2)	−0.0155 (14)	0.0041 (15)	0.0079 (16)
C20	0.069 (2)	0.0501 (19)	0.056 (2)	−0.0055 (16)	0.0151 (17)	0.0068 (16)
C21	0.092 (3)	0.0519 (19)	0.0412 (18)	−0.0117 (18)	−0.0012 (17)	0.0006 (15)
C22	0.069 (2)	0.0464 (17)	0.0483 (18)	−0.0188 (15)	−0.0086 (15)	−0.0026 (14)

Geometric parameters (Å, º)

S1—O2	1.558 (3)	C4—C5	1.525 (4)
S1—O3	1.396 (4)	C4—H41	0.942
S1—O4	1.412 (3)	C5—C6	1.553 (4)
S1—C14	1.847 (5)	C5—C13	1.536 (5)
S101—O102	1.574 (18)	C5—H51	0.974
S101—O103	1.416 (19)	C6—C7	1.538 (4)
S101—O104	1.406 (19)	C6—H61	0.996

S101—C114	1.811 (17)	C6—H62	0.948
F1—C14	1.308 (5)	C7—C8	1.505 (4)
F2—C14	1.293 (6)	C7—C12	1.578 (3)
F3—C14	1.329 (6)	C8—C9	1.330 (4)
F101—C114	1.314 (19)	C8—H81	0.960
F102—C114	1.315 (19)	C9—C10	1.501 (4)
F103—C114	1.303 (19)	C9—H91	0.948
O1—C1	1.355 (4)	C10—C11	1.520 (4)
O1—C11	1.450 (4)	C10—H101	0.980
O2—C3	1.446 (4)	C11—C12	1.545 (4)
O5—C15	1.207 (3)	C11—H111	0.987
O6—C16	1.209 (3)	C12—C13	1.529 (4)
O102—C3	1.445 (18)	C13—H131	0.990
N1—N2	1.438 (3)	C13—H132	0.982
N1—C10	1.462 (4)	C17—C18	1.380 (4)
N1—C15	1.383 (3)	C17—C22	1.387 (4)
N2—C7	1.500 (3)	C18—C19	1.389 (4)
N2—C16	1.389 (3)	C18—H181	0.932
N3—C15	1.384 (4)	C19—C20	1.370 (5)
N3—C16	1.394 (4)	C19—H191	0.943
N3—C17	1.433 (3)	C20—C21	1.377 (5)
C1—C2	1.327 (4)	C20—H201	0.965
C1—H11	0.922	C21—C22	1.387 (4)
C2—C3	1.428 (4)	C21—H211	0.940
C2—C12	1.520 (4)	C22—H221	0.926
C3—C4	1.305 (4)		
F1···F3^{i}	3.014 (4)	O2···O4^{iv}	3.256 (5)
F1···O103^{i}	3.17 (3)	O2···O102^{iv}	3.41 (3)
F1···C20^{ii}	3.483 (4)	O3···C21^{vi}	3.448 (6)
F2···F103^{iii}	3.06 (4)	O4···C1^{viii}	3.345 (4)
F2···C1^{iv}	3.149 (5)	O4···C3^{iv}	3.467 (4)
F2···C21^{v}	3.499 (4)	O4···O102^{iv}	3.49 (3)
F2···C9^{iv}	3.517 (4)	O4···C8^{iv}	3.509 (4)
F2···O1^{iv}	3.560 (4)	O5···C18^{vii}	3.149 (4)
F3···F3^{i}	3.356 (5)	O5···C19^{vii}	3.194 (4)
F101···C21^{vi}	3.19 (5)	O5···O5^{ix}	3.226 (5)
F101···C22^{vi}	3.37 (4)	O5···C15^{ix}	3.341 (4)
F101···C4^{vii}	3.48 (4)	O5···C9^{ix}	3.444 (4)
F102···F102^{viii}	2.79 (6)	O6···C6^{x}	3.303 (3)
F102···C1^{viii}	3.14 (4)	O6···C5^{x}	3.336 (4)
F102···O4^{viii}	3.41 (3)	O6···C11^{iii}	3.381 (4)
F103···C21^{vi}	3.52 (4)	O6···O6^{x}	3.542 (4)
F103···C20^{ii}	3.57 (4)	O103···C21^{vi}	3.25 (4)
O1···C8^{vii}	3.408 (3)	O103···C22^{vi}	3.37 (4)
O1···O4^{viii}	3.474 (3)	O104···C8^{iv}	3.54 (3)
O2···O2^{iv}	3.102 (8)	O104···C9^{iv}	3.57 (3)
O2—S1—O3	111.83 (18)	C10—C9—H91	121.7
O2—S1—O4	107.27 (18)	C9—C10—N1	108.7 (2)
O3—S1—O4	122.0 (2)	C9—C10—C11	110.4 (2)
O2—S1—C14	99.9 (2)	N1—C10—C11	104.0 (3)
O3—S1—C14	108.3 (2)	C9—C10—H101	113.8
O4—S1—C14	105.1 (2)	N1—C10—H101	109.5

O102—S101—O103	110.0 (19)
O102—S101—O104	112 (2)
O103—S101—O104	124 (2)
O102—S101—C114	95.4 (17)
O103—S101—C114	100.3 (18)
O104—S101—C114	110 (2)
C1—O1—C11	107.6 (2)
S1—O2—C3	121.4 (2)
S101—O102—C3	127.3 (19)
N2—N1—C10	111.7 (2)
N2—N1—C15	108.6 (2)
C10—N1—C15	121.1 (3)
N1—N2—C7	112.5 (2)
N1—N2—C16	107.5 (2)
C7—N2—C16	123.9 (2)
C15—N3—C16	111.7 (2)
C15—N3—C17	124.2 (2)
C16—N3—C17	124.0 (2)
O1—C1—C2	115.2 (3)
O1—C1—H11	119.2
C2—C1—H11	125.6
C1—C2—C3	132.1 (3)
C1—C2—C12	109.1 (3)
C3—C2—C12	117.9 (2)
O2—C3—C2	114.5 (3)
O102—C3—C2	128.7 (16)
O2—C3—C4	122.4 (3)
O102—C3—C4	108.2 (16)
C2—C3—C4	123.0 (3)
C3—C4—C5	116.6 (3)
C3—C4—H41	122.3
C5—C4—H41	121.0
C4—C5—C6	107.8 (3)
C4—C5—C13	110.4 (3)
C6—C5—C13	104.1 (2)
C4—C5—H51	110.5
C6—C5—H51	111.9
C13—C5—H51	111.9
C5—C6—C7	104.7 (2)
C5—C6—H61	110.2
C7—C6—H61	109.8
C5—C6—H62	110.0
C7—C6—H62	110.5
H61—C6—H62	111.4
C6—C7—N2	110.0 (2)
C6—C7—C8	122.4 (2)
N2—C7—C8	105.3 (2)
C6—C7—C12	104.3 (2)
N2—C7—C12	104.8 (2)
C8—C7—C12	108.8 (2)
C7—C8—C9	113.2 (3)
C7—C8—H81	122.1
C9—C8—H81	124.6
C8—C9—C10	114.9 (3)
C11—C10—H101	109.9
C10—C11—O1	109.2 (3)
C10—C11—C12	108.7 (2)
O1—C11—C12	107.1 (2)
C10—C11—H111	109.4
O1—C11—H111	110.6
C12—C11—H111	111.7
C11—C12—C2	101.0 (2)
C11—C12—C7	109.4 (2)
C2—C12—C7	113.5 (2)
C11—C12—C13	126.0 (3)
C2—C12—C13	107.2 (2)
C7—C12—C13	100.1 (2)
C5—C13—C12	99.3 (2)
C5—C13—H131	113.4
C12—C13—H131	112.9
C5—C13—H132	111.5
C12—C13—H132	107.8
H131—C13—H132	111.2
S1—C14—F3	108.6 (3)
S1—C14—F1	108.1 (3)
F3—C14—F1	108.5 (4)
S1—C14—F2	111.0 (3)
F3—C14—F2	109.7 (4)
F1—C14—F2	110.9 (4)
N3—C15—N1	105.3 (2)
N3—C15—O5	128.2 (3)
N1—C15—O5	126.5 (3)
N3—C16—N2	105.2 (2)
N3—C16—O6	126.4 (2)
N2—C16—O6	128.2 (3)
N3—C17—C18	120.0 (3)
N3—C17—C22	119.1 (3)
C18—C17—C22	120.8 (3)
C17—C18—C19	119.2 (3)
C17—C18—H181	120.3
C19—C18—H181	120.5
C18—C19—C20	120.4 (3)
C18—C19—H191	118.8
C20—C19—H191	120.9
C19—C20—C21	120.2 (3)
C19—C20—H201	120.1
C21—C20—H201	119.7
C20—C21—C22	120.5 (3)
C20—C21—H211	120.9
C22—C21—H211	118.6
C17—C22—C21	118.9 (3)
C17—C22—H221	119.1
C21—C22—H221	122.0
S101—C114—F102	107.2 (19)
S101—C114—F101	111 (2)
F102—C114—F101	111 (2)
S101—C114—F103	105 (2)
F102—C114—F103	112 (2)

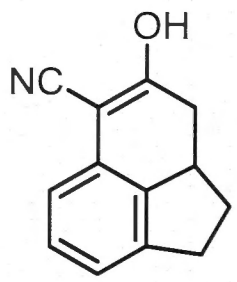
C8—C9—H91	123.4	F101—C114—F103	111 (2)
S1—O2—C3—C2	89.2 (4)	N2—C16—N3—C17	−169.8 (3)
S1—O2—C3—C4	−94.4 (4)	N3—C15—N1—C10	137.0 (3)
S101—O102—C3—O2	140 (8)	N3—C16—N2—C7	−142.9 (2)
S101—O102—C3—C2	114 (2)	N3—C17—C18—C19	179.9 (2)
S101—O102—C3—C4	−62 (3)	N3—C17—C22—C21	179.8 (3)
F1—C14—S1—O2	171.2 (3)	C1—O1—C11—C10	−119.1 (3)
F1—C14—S1—O3	−71.7 (4)	C1—O1—C11—C12	−1.6 (3)
F1—C14—S1—O4	60.1 (4)	C1—C2—C3—C4	167.6 (4)
F2—C14—S1—O2	49.5 (3)	C1—C2—C12—C7	117.0 (3)
F2—C14—S1—O3	166.6 (3)	C1—C2—C12—C11	0.0 (4)
F2—C14—S1—O4	−61.6 (3)	C1—C2—C12—C13	−133.4 (3)
F3—C14—S1—O2	−71.2 (4)	C2—C1—O1—C11	1.7 (4)
F3—C14—S1—O3	45.9 (4)	C2—C3—C4—C5	0.0 (5)
F3—C14—S1—O4	177.7 (3)	C2—C12—C7—C6	75.4 (3)
F101—C114—S101—O102	65 (3)	C2—C12—C7—C8	−56.7 (3)
F101—C114—S101—O103	−46 (3)	C2—C12—C11—C10	118.7 (3)
F101—C114—S101—O104	−179 (4)	C2—C12—C13—C5	−67.4 (3)
F102—C114—S101—O102	−56 (3)	C3—O2—S1—C14	104.7 (3)
F102—C114—S101—O103	−167 (3)	C3—O102—S101—C114	−78 (3)
F102—C114—S101—O104	60 (3)	C3—C2—C12—C7	−72.5 (4)
F103—C114—S101—O102	−175 (3)	C3—C2—C12—C11	170.6 (3)
F103—C114—S101—O103	74 (3)	C3—C2—C12—C13	37.2 (4)
F103—C114—S101—O104	−59 (4)	C3—C4—C5—C6	75.9 (4)
O1—C1—C2—C3	−169.8 (4)	C3—C4—C5—C13	−37.1 (5)
O1—C1—C2—C12	−1.1 (4)	C4—C3—C2—C12	−0.3 (5)
O1—C11—C10—N1	179.2 (2)	C4—C5—C6—C7	−95.7 (3)
O1—C11—C10—C9	62.7 (3)	C4—C5—C13—C12	69.6 (3)
O1—C11—C12—C2	0.9 (3)	C5—C6—C7—C8	134.1 (2)
O1—C11—C12—C7	−119.0 (3)	C5—C6—C7—C12	10.3 (3)
O1—C11—C12—C13	121.9 (3)	C5—C13—C12—C7	51.2 (2)
O2—C3—C2—C1	−16.1 (6)	C5—C13—C12—C11	174.4 (3)
O2—C3—C2—C12	176.0 (3)	C6—C5—C13—C12	−45.8 (3)
O2—C3—C4—C5	−176.0 (4)	C6—C7—N2—C16	−60.2 (3)
O3—S1—O2—C3	−9.7 (4)	C6—C7—C8—C9	−177.7 (2)
O4—S1—O2—C3	−146.0 (3)	C6—C7—C12—C11	−172.7 (2)
O5—C15—N1—N2	−176.1 (3)	C6—C7—C12—C13	−38.5 (3)
O5—C15—N1—C10	−44.9 (5)	C7—N2—N1—C10	5.7 (3)
O5—C15—N3—C16	170.0 (3)	C7—N2—N1—C15	141.8 (3)
O5—C15—N3—C17	−7.0 (5)	C7—C6—C5—C13	21.6 (3)
O6—C16—N2—N1	174.8 (3)	C7—C8—C9—C10	−0.5 (3)
O6—C16—N2—C7	40.8 (4)	C7—C12—C11—C10	−1.2 (3)
O6—C16—N3—C15	−170.5 (3)	C8—C7—N2—C16	73.6 (3)
O6—C16—N3—C17	6.5 (5)	C8—C7—C12—C11	55.2 (3)
O102—C3—C2—C1	−9 (2)	C8—C7—C12—C13	−170.6 (2)
O102—C3—C2—C12	−177 (2)	C8—C9—C10—C11	58.8 (3)
O102—C3—C4—C5	177 (2)	C9—C8—C7—C12	−56.1 (3)
N1—N2—C7—C6	167.8 (2)	C9—C10—N1—C15	−80.1 (3)
N1—N2—C7—C8	−58.4 (3)	C9—C10—C11—C12	−53.8 (3)
N1—N2—C7—C12	56.3 (3)	C10—N1—N2—C16	−134.0 (3)
N1—N2—C16—N3	−9.0 (3)	C10—C11—C12—C13	−120.3 (3)
N1—C10—C9—C8	−54.7 (3)	C11—C10—N1—C15	162.2 (2)
N1—C10—C11—C12	62.7 (3)	C12—C7—N2—C16	−171.7 (2)

N1—C15—N3—C16	−11.9 (4)	C15—N1—N2—C16	2.1 (3)
N1—C15—N3—C17	171.1 (3)	C15—N3—C17—C18	116.4 (3)
N2—N1—C10—C9	49.8 (3)	C15—N3—C17—C22	−64.1 (4)
N2—N1—C10—C11	−67.8 (3)	C16—N3—C17—C18	−60.2 (4)
N2—N1—C15—N3	5.8 (3)	C16—N3—C17—C22	119.3 (3)
N2—C7—C6—C5	−101.5 (2)	C17—C18—C19—C20	0.4 (5)
N2—C7—C8—C9	55.8 (3)	C17—C22—C21—C20	0.3 (5)
N2—C7—C12—C2	−169.0 (2)	C18—C17—C22—C21	−0.7 (4)
N2—C7—C12—C11	−57.1 (3)	C18—C19—C20—C21	−0.9 (5)
N2—C7—C12—C13	77.1 (2)	C19—C18—C17—C22	0.4 (4)
N2—C16—N3—C15	13.2 (3)	C19—C20—C21—C22	0.5 (5)

Symmetry codes: (i) $-x+1, -y, -z+2$; (ii) $x-1, y-1, z+1$; (iii) $x+1, y, z$; (iv) $-x+1, -y+1, -z+2$; (v) $x, y-1, z+1$; (vi) $-x+1, -y+1, -z+1$; (vii) $x-1, y, z$; (viii) $-x, -y+1, -z+2$; (ix) $-x+1, -y+2, -z+1$; (x) $-x+2, -y+1, -z+1$.

Appendix 7

X-ray Crystal Structure Report for Compound 4.82.



Crystal structure of $C_{13}H_{11}NO$ — ban1111

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Abstract

The crystal structure of $C_{13}H_{11}NO$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{13}H_{11}NO$. There is disorder in part of the structure.

Experimental

The compound was prepared by NH and crystallized from dichloromethane. The sample ID is NH7-16-f2.

Refinement

There are two alternative locations for C6, one above the plane of the other atoms of the structure, and the other below it. The relative occupancies of the two sites (C6 and C61) were refined. Restraints were imposed on bonding distances involving these two sites so corresponding bonds should tend to have similar lengths. Even with these restraints there are significant differences in the distances, suggesting that the disorder extends beyond just C6. However, it was decided not to split C5 and C7 also, as their two sites would be very close together and not really resolvable.

The alcohol H atom was located in a difference electron density map. It was included at this position and then its coordinates were refined. Other H atoms were included at geometrically determined positions and were constrained to ride on the atoms to which they were respectively attached.

The largest peaks in the final difference electron density map are mainly located near the disorder.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*-II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Molecular Structure Corporation. (1992–1997). *TEXSAN*. Single Crystal Structure Analysis Software. Version 1.8. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Johnson, C. K. (1976). *ORTEP*II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.

(ban1111)

Crystal data

$C_{13}H_{11}NO$
$M_r = 197.24$
Monoclinic, $P2_1/c$
$a = 8.0941\ (2)$ Å
$b = 8.6997\ (3)$ Å
$c = 14.5554\ (5)$ Å
$\beta = 103.163\ (2)°$
$V = 998.01\ (6)$ Å^3
$Z = 4$

$F(000) = 416$
$D_x = 1.313$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 14278 reflections
$\theta = 2.6–27.5°$
$\mu = 0.08$ mm^{-1}
$T = 200$ K
Prism, Yellow
0.23 × 0.10 × 0.09 mm

Data collection

Nonius KappaCCD diffractometer
graphite
φ and ω scans with CCD
Absorption correction: Multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)
$T_{min} = 0.89$, $T_{max} = 0.99$
19420 measured reflections
2292 independent reflections

1847 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.042$
$\theta_{max} = 27.5°$, $\theta_{min} = 2.6°$
$h = -9 \rightarrow 10$
$k = -11 \rightarrow 11$
$l = -18 \rightarrow 18$

Refinement

Refinement on F^2
Least-squares matrix: Full

Primary atom site location: Structure-invariant direct methods
Hydrogen site location: Inferred from neighbouring sites

$R[F^2 > 2\sigma(F^2)] = 0.059$

$wR(F^2) = 0.160$

$S = 1.00$
2291 reflections
149 parameters
6 restraints

H atoms treated by a mixture of independent and constrained refinement
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.08P)^2 + 0.47P]$,
where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.004$
$\Delta\rho_{max} = 0.29$ e Å^{-3}
$\Delta\rho_{min} = -0.30$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
O4	0.4174 (2)	0.39099 (16)	0.74549 (9)	0.0537	
N15	0.4882 (3)	0.0983 (2)	0.60931 (12)	0.0594	
C1	0.4280 (3)	0.2182 (2)	0.59688 (12)	0.0474	
C2	0.3547 (2)	0.3673 (2)	0.58289 (12)	0.0408	
C3	0.3539 (2)	0.4538 (2)	0.66021 (12)	0.0390	
C5	0.2836 (3)	0.6126 (2)	0.65442 (13)	0.0534	
C6	0.2683 (5)	0.6943 (4)	0.5631 (2)	0.0379	0.524 (8)
C7	0.1404 (3)	0.8168 (2)	0.52712 (14)	0.0508	
C8	0.0948 (3)	0.8083 (3)	0.41941 (15)	0.0593	
C9	0.1502 (2)	0.6490 (2)	0.39826 (13)	0.0449	
C10	0.1431 (2)	0.5710 (2)	0.31432 (13)	0.0483	
C11	0.2059 (2)	0.4223 (2)	0.31787 (13)	0.0487	
C12	0.2754 (2)	0.3493 (2)	0.40312 (12)	0.0404	
C13	0.2842 (2)	0.4275 (2)	0.48753 (12)	0.0396	
C14	0.2222 (3)	0.5756 (2)	0.48198 (13)	0.0536	
C61	0.1692 (6)	0.6529 (4)	0.5665 (2)	0.0393	0.476 (8)
H41	0.431 (3)	0.467 (3)	0.7875 (18)	0.0650*	
H51	0.3553	0.6723	0.7020	0.0641*	0.524
H52	0.1735	0.6069	0.6668	0.0641*	0.524
H53	0.2242	0.6241	0.7033	0.0641*	0.476
H54	0.3762	0.6825	0.6645	0.0641*	0.476
H61	0.3769	0.7348	0.5622	0.0454*	0.524
H71	0.1870	0.9149	0.5468	0.0610*	0.524
H72	0.0417	0.8006	0.5508	0.0610*	0.524
H73	0.0502	0.8636	0.5488	0.0610*	0.476
H74	0.2410	0.8756	0.5476	0.0610*	0.476
H81	0.1543	0.8844	0.3929	0.0712*	
H82	−0.0238	0.8211	0.3956	0.0712*	
H101	0.0959	0.6186	0.2554	0.0579*	
H111	0.2015	0.3687	0.2605	0.0585*	
H121	0.3165	0.2469	0.4036	0.0485*	
H611	0.0610	0.6127	0.5687	0.0471*	0.476

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O4	0.0852 (10)	0.0410 (7)	0.0326 (7)	−0.0047 (7)	0.0086 (6)	0.0007 (5)
N15	0.0866 (13)	0.0457 (10)	0.0417 (9)	0.0113 (9)	0.0057 (8)	0.0004 (7)
C1	0.0615 (11)	0.0459 (11)	0.0322 (8)	0.0037 (9)	0.0051 (7)	−0.0012 (8)

C2	0.0462 (9)	0.0398 (9)	0.0350 (9)	0.0030 (7)	0.0061 (7)	−0.0015 (7)
C3	0.0430 (9)	0.0393 (9)	0.0348 (8)	−0.0074 (7)	0.0090 (7)	−0.0001 (7)
C5	0.0777 (14)	0.0415 (10)	0.0413 (10)	0.0020 (9)	0.0143 (9)	−0.0039 (8)
C6	0.034 (2)	0.0361 (18)	0.0427 (18)	−0.0039 (15)	0.0061 (13)	−0.0027 (14)
C7	0.0533 (11)	0.0434 (10)	0.0542 (11)	0.0032 (8)	0.0090 (9)	0.0000 (9)
C8	0.0616 (12)	0.0551 (13)	0.0551 (12)	0.0157 (10)	0.0007 (9)	0.0033 (10)
C9	0.0417 (9)	0.0478 (10)	0.0423 (10)	0.0021 (8)	0.0034 (7)	0.0027 (8)
C10	0.0482 (10)	0.0590 (12)	0.0355 (9)	−0.0017 (9)	0.0049 (7)	0.0056 (8)
C11	0.0527 (10)	0.0593 (12)	0.0341 (9)	−0.0040 (9)	0.0097 (8)	−0.0065 (8)
C12	0.0392 (8)	0.0447 (9)	0.0377 (9)	−0.0024 (7)	0.0095 (7)	−0.0052 (7)
C13	0.0395 (9)	0.0440 (9)	0.0337 (8)	0.0020 (7)	0.0055 (6)	−0.0021 (7)
C14	0.0659 (12)	0.0535 (12)	0.0360 (9)	0.0185 (10)	0.0005 (8)	−0.0044 (8)
C61	0.038 (3)	0.038 (2)	0.041 (2)	0.0024 (18)	0.0085 (15)	−0.0026 (15)

Geometric parameters (Å, º)

O4—C3	1.346 (2)	C7—H71	0.950
O4—H41	0.89 (3)	C7—H72	0.950
N15—C1	1.148 (3)	C7—H73	0.950
C1—C2	1.422 (3)	C7—H74	0.950
C2—C3	1.355 (2)	C8—C9	1.509 (3)
C2—C13	1.472 (2)	C8—H81	0.950
C3—C5	1.490 (3)	C8—H82	0.950
C5—C6	1.487 (3)	C9—C10	1.387 (3)
C5—C61	1.441 (3)	C9—C14	1.382 (3)
C5—H51	0.950	C10—C11	1.387 (3)
C5—H52	0.950	C10—H101	0.950
C5—H53	0.950	C11—C12	1.394 (3)
C5—H54	0.950	C11—H111	0.950
C6—C7	1.495 (3)	C12—C13	1.392 (2)
C6—C14	1.549 (4)	C12—H121	0.950
C6—C61	0.891 (4)	C13—C14	1.379 (3)
C6—H61	0.950	C14—C61	1.546 (4)
C7—C8	1.529 (3)	C61—H611	0.950
C7—C61	1.535 (3)		

O4···N15^{i}	2.751 (2)	N15···C5^{iii}	3.516 (2)
O4···C12^{ii}	3.487 (2)	N15···C3^{iii}	3.538 (2)
O4···C5^{iii}	3.499 (2)	N15···C8^{iv}	3.588 (4)
O4···C11^{ii}	3.506 (2)	C1···C9^{iv}	3.590 (3)

C3—O4—H41	107.2 (16)	C8—C7—H74	109.7
N15—C1—C2	179.15 (19)	C61—C7—H74	109.7
C1—C2—C3	117.92 (16)	H73—C7—H74	109.5
C1—C2—C13	121.27 (16)	C7—C8—C9	103.91 (16)
C3—C2—C13	120.80 (16)	C7—C8—H81	110.8
C2—C3—O4	117.89 (17)	C9—C8—H81	110.8
C2—C3—C5	122.81 (16)	C7—C8—H82	110.8
O4—C3—C5	119.29 (15)	C9—C8—H82	110.8
C3—C5—C6	116.55 (18)	H81—C8—H82	109.5
C3—C5—C61	115.83 (19)	C8—C9—C10	132.37 (18)

C3—C5—H51	107.7
C6—C5—H51	107.7
C3—C5—H52	107.7
C6—C5—H52	107.7
H51—C5—H52	109.5
C3—C5—H53	107.9
C61—C5—H53	107.9
C3—C5—H54	107.9
C61—C5—H54	107.9
H53—C5—H54	109.5
C5—C6—C7	124.3 (3)
C5—C6—C14	108.6 (2)
C7—C6—C14	100.4 (2)
C5—C6—H61	107.5
C7—C6—H61	107.5
C14—C6—H61	107.5
C6—C7—C8	108.10 (18)
C8—C7—C61	108.58 (19)
C6—C7—H71	109.8
C8—C7—H71	109.8
C6—C7—H72	109.8
C8—C7—H72	109.8
H71—C7—H72	109.5
C8—C7—H73	109.7
C61—C7—H73	109.7
C8—C9—C14	109.26 (17)
C10—C9—C14	118.37 (18)
C9—C10—C11	118.83 (17)
C9—C10—H101	120.6
C11—C10—H101	120.6
C10—C11—C12	121.93 (17)
C10—C11—H111	119.0
C12—C11—H111	119.0
C11—C12—C13	119.47 (18)
C11—C12—H121	120.3
C13—C12—H121	120.3
C2—C13—C12	126.13 (17)
C2—C13—C14	116.45 (16)
C12—C13—C14	117.42 (16)
C6—C14—C9	110.10 (19)
C6—C14—C13	123.88 (18)
C9—C14—C13	123.97 (18)
C9—C14—C61	111.29 (19)
C13—C14—C61	121.55 (19)
C7—C61—C14	98.8 (2)
C7—C61—C5	124.7 (3)
C14—C61—C5	111.2 (3)
C7—C61—H611	106.9
C14—C61—H611	106.9
C5—C61—H611	106.9

O4—C3—C2—C1	−2.2 (3)
O4—C3—C2—C13	178.8 (2)
O4—C3—C5—C6	160.6 (2)
O4—C3—C5—C61	−159.9 (3)
C1—C2—C3—C5	178.9 (2)
C1—C2—C13—C12	2.1 (3)
C1—C2—C13—C14	−177.6 (2)
C2—C3—C5—C6	−20.5 (3)
C2—C3—C5—C61	19.0 (3)
C2—C13—C12—C11	−179.5 (2)
C2—C13—C14—C6	18.6 (3)
C2—C13—C14—C9	−179.3 (2)
C2—C13—C14—C61	−21.3 (3)
C3—C2—C13—C12	−179.0 (2)
C3—C2—C13—C14	1.4 (3)
C3—C5—C6—C7	152.3 (2)
C3—C5—C6—C14	34.9 (3)
C3—C5—C61—C7	−152.9 (3)
C3—C5—C61—C14	−34.9 (4)
C5—C3—C2—C13	−0.2 (3)
C5—C6—C7—C8	−148.6 (3)
C5—C6—C14—C9	159.2 (2)
C5—C6—C14—C13	−36.6 (4)
C5—C61—C7—C8	149.8 (3)
C5—C61—C14—C9	−160.9 (2)
C5—C61—C14—C13	38.6 (4)
C6—C7—C8—C9	19.1 (3)
C6—C14—C9—C8	−16.5 (3)
C6—C14—C9—C10	162.6 (2)
C6—C14—C13—C12	−161.1 (2)
C7—C6—C5—C61	54.4 (4)
C7—C6—C14—C9	27.4 (3)
C7—C6—C14—C13	−168.4 (2)
C7—C8—C9—C10	179.7 (2)
C7—C8—C9—C14	−1.3 (2)
C7—C61—C14—C9	−28.1 (3)
C7—C61—C14—C13	171.4 (2)
C8—C7—C6—C14	−27.3 (3)
C8—C7—C61—C14	26.2 (3)
C8—C9—C10—C11	179.9 (2)
C8—C9—C14—C13	179.2 (2)
C8—C9—C14—C61	19.3 (3)
C9—C8—C7—C61	−16.9 (3)
C9—C10—C11—C12	0.1 (3)
C9—C14—C13—C12	1.0 (3)
C10—C9—C14—C13	−1.6 (3)
C10—C9—C14—C61	−161.6 (2)
C10—C11—C12—C13	−0.7 (3)
C11—C10—C9—C14	1.0 (3)
C11—C12—C13—C14	0.1 (3)
C12—C13—C14—C61	159.0 (2)

Symmetry codes: (i) $-x+1, y+1/2, -z+3/2$; (ii) $x, -y+1/2, z+1/2$; (iii) $-x+1, y-1/2, -z+3/2$; (iv) $-x+1, -y+1, -z+1$.

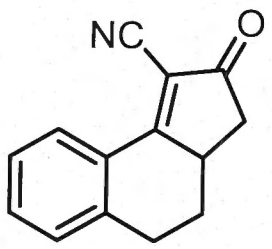
Hydrogen-bond geometry (Å, °)

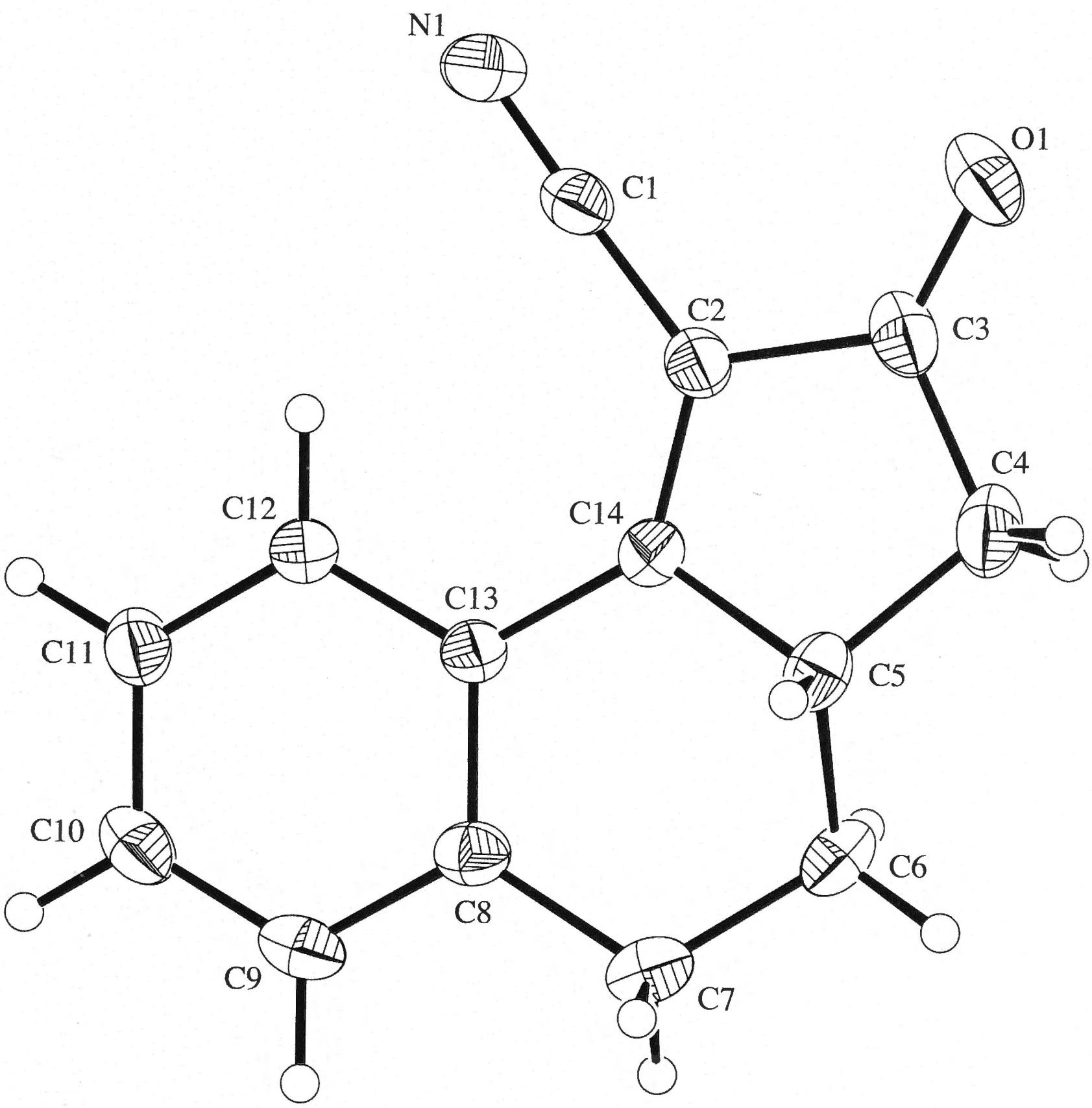
D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H41···N15^{i}	0.89 (3)	1.88 (3)	2.751 (3)	165 (2)

Symmetry code: (i) $-x+1, y+1/2, -z+3/2$.

Appendix 8

X-ray Crystal Structure Report for Compound 4.95.





Crystal structure of $C_{14}H_{11}NO$ — ban1246

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Abstract

The crystal structure of $C_{14}H_{11}NO$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{14}H_{11}NO$. There is some disorder in the packing of the molecules.

Experimental

The compound was prepared by NH and crystallized from pentane/ether. The sample ID is NH7-31A-f2-recolf2.

Refinement

Direct methods gave the major locations for all non-H atoms. Alternative sites for C5 and C6 were observed in difference electron density maps. These sites, C51 and C61, were included in the structural model. They indicate a packing disorder of molecules differing in configuration at C5. The relative occupancies of the two configurations have been refined. Restraints were applied to bonding distances involving the disordered sites so corresponding values would tend to their means. Note that the molecules at crystallographic inversion-related positions have the reversed configurations of molecules, so the crystal is racemic.

Hydrogen atoms were included at idealized positions and ride on the atoms to which they are bonded.

The largest peaks in the final difference electron density map are located near C14, midway along C—C bonds or randomly through the structure.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*-II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Mackay, S., Gilmore, C. J., Edwards, C., Stewart, N. & Shankland, K. (2000). *maXus* Computer Program for the Solution and Refinement of Crystal Structures. Nonius, The Netherlands, MacScience, Japan & The University of Glasgow.

Coppens, P. (1970). The Evaluation of Absorption and Extinction in Single-Crystal Structure Analysis. Crystallographic Computing. F. R. Ahmed, S. R. Hall and C. P. Huber, eds., Munksgaard. Copenhagen. pp 255-270.

Molecular Structure Corporation. (1992–1997). *TEXSAN*. Single Crystal Structure Analysis Software. Version 1.8. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Johnson, C. K. (1976). *ORTEP*II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.

(ban1246)

Crystal data

$C_{14}H_{11}NO$
$M_r = 209.25$
Monoclinic, $P2_1/n$
$a = 9.4850\ (2)$ Å
$b = 7.3212\ (2)$ Å
$c = 15.2014\ (4)$ Å
$\beta = 93.1007\ (16)°$
$V = 1054.06\ (5)$ Å^3
$Z = 4$
$F(000) = 440$
$D_x = 1.318$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 13311 reflections
$\theta = 2.6$–$27.5°$
$\mu = 0.08$ mm^{-1}
$T = 200$ K
Block, Colourless
0.42 × 0.36 × 0.18 mm

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
φ and ω scans with CCD
Absorption correction: Integration via Gaussian method (Coppens, 1970) implemented in *maXus* (2000)
$T_{min} = 0.969$, $T_{max} = 0.988$
21785 measured reflections
2424 independent reflections
1942 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.037$
$\theta_{max} = 27.5°$, $\theta_{min} = 2.6°$
$h = -12 \rightarrow 12$
$k = -9 \rightarrow 9$
$l = -19 \rightarrow 19$

Refinement

Refinement on F^2
Least-squares matrix: Full
$R[F^2 > 2\sigma(F^2)] = 0.047$
$wR(F^2) = 0.127$
$S = 0.98$
2423 reflections
164 parameters
28 restraints
Primary atom site location: Structure-invariant direct methods
Hydrogen site location: Inferred from neighbouring sites
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.07P)^2 + 0.29P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.0002$
$\Delta\rho_{max} = 0.20$ e Å^{-3}
$\Delta\rho_{min} = -0.28$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
O1	0.08493 (12)	0.45324 (17)	0.59892 (7)	0.0626	
N1	0.31356 (16)	0.8492 (2)	0.56200 (9)	0.0590	
C1	0.28924 (14)	0.7089 (2)	0.53067 (9)	0.0426	
C2	0.25463 (14)	0.53504 (19)	0.49371 (9)	0.0415	
C3	0.14974 (15)	0.4161 (2)	0.53445 (10)	0.0501	
C4	0.14125 (18)	0.2437 (2)	0.48153 (13)	0.0592	
C5	0.2135 (3)	0.2852 (3)	0.39531 (19)	0.0432	0.671 (7)
C6	0.3127 (3)	0.1385 (3)	0.3642 (2)	0.0480	0.671 (7)
C7	0.38577 (18)	0.2079 (2)	0.28398 (11)	0.0546	
C8	0.45220 (14)	0.39437 (19)	0.29618 (9)	0.0417	

C9	0.55513 (16)	0.4507 (2)	0.24025 (9)	0.0520	
C10	0.61892 (16)	0.6194 (2)	0.24933 (10)	0.0529	
C11	0.58093 (15)	0.7371 (2)	0.31507 (10)	0.0473	
C12	0.47987 (15)	0.68468 (19)	0.37141 (9)	0.0441	
C13	0.41310 (14)	0.51354 (18)	0.36296 (8)	0.0389	
C14	0.30486 (16)	0.4555 (2)	0.42142 (10)	0.0490	
C51	0.2812 (7)	0.2481 (6)	0.4284 (4)	0.0427	0.329 (7)
C61	0.2583 (7)	0.1896 (9)	0.3339 (4)	0.0551	0.329 (7)
H41	0.1891	0.1476	0.5127	0.0710*	0.671
H42	0.0455	0.2103	0.4692	0.0710*	0.671
H43	0.1399	0.1397	0.5188	0.0710*	0.329
H44	0.0596	0.2433	0.4425	0.0710*	0.329
H51	0.1450	0.3154	0.3497	0.0519*	0.671
H61	0.3815	0.1109	0.4100	0.0575*	0.671
H62	0.2603	0.0315	0.3489	0.0575*	0.670
H71	0.4577	0.1235	0.2709	0.0655*	0.671
H72	0.3179	0.2139	0.2358	0.0655*	0.671
H73	0.4522	0.1177	0.3037	0.0655*	0.329
H74	0.3612	0.1898	0.2232	0.0655*	0.329
H91	0.5821	0.3711	0.1948	0.0623*	
H101	0.6890	0.6548	0.2104	0.0634*	
H111	0.6245	0.8536	0.3213	0.0568*	
H121	0.4547	0.7655	0.4169	0.0529*	
H511	0.3581	0.1867	0.4581	0.0513*	0.329
H611	0.2295	0.0653	0.3326	0.0661*	0.329
H612	0.1858	0.2631	0.3066	0.0661*	0.329

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0552 (6)	0.0759 (8)	0.0587 (7)	0.0111 (6)	0.0218 (5)	0.0206 (6)
N1	0.0753 (9)	0.0545 (8)	0.0486 (7)	0.0059 (7)	0.0142 (6)	−0.0083 (6)
C1	0.0460 (7)	0.0455 (8)	0.0371 (7)	0.0093 (6)	0.0092 (5)	0.0026 (6)
C2	0.0425 (7)	0.0390 (7)	0.0438 (7)	0.0063 (5)	0.0099 (5)	0.0059 (6)
C3	0.0436 (8)	0.0522 (9)	0.0556 (8)	0.0081 (6)	0.0127 (6)	0.0175 (7)
C4	0.0515 (9)	0.0458 (9)	0.0818 (11)	−0.0039 (7)	0.0168 (8)	0.0130 (8)
C5	0.0377 (14)	0.0356 (11)	0.0558 (14)	0.0000 (9)	−0.0037 (11)	0.0042 (10)
C6	0.0479 (15)	0.0304 (12)	0.0649 (17)	0.0001 (10)	−0.0028 (12)	−0.0040 (11)
C7	0.0637 (9)	0.0446 (8)	0.0552 (9)	0.0036 (7)	0.0000 (7)	−0.0140 (7)
C8	0.0444 (7)	0.0411 (7)	0.0396 (7)	0.0083 (6)	0.0015 (5)	−0.0030 (5)
C9	0.0539 (9)	0.0618 (10)	0.0411 (7)	0.0104 (7)	0.0111 (6)	−0.0080 (7)
C10	0.0483 (8)	0.0642 (10)	0.0475 (8)	0.0038 (7)	0.0161 (6)	0.0052 (7)
C11	0.0454 (7)	0.0448 (8)	0.0527 (8)	−0.0007 (6)	0.0105 (6)	0.0064 (6)
C12	0.0504 (8)	0.0365 (7)	0.0466 (7)	0.0017 (6)	0.0137 (6)	−0.0022 (6)
C13	0.0433 (7)	0.0336 (6)	0.0407 (7)	0.0043 (5)	0.0090 (5)	−0.0003 (5)
C14	0.0581 (9)	0.0345 (7)	0.0560 (9)	−0.0026 (6)	0.0192 (7)	−0.0029 (6)
C51	0.039 (3)	0.035 (2)	0.054 (3)	−0.0022 (19)	0.000 (2)	0.0025 (19)
C61	0.055 (3)	0.041 (3)	0.068 (4)	−0.006 (2)	−0.009 (3)	−0.011 (3)

Geometric parameters (Å, º)

O1—C3	1.2154 (18)	C7—H71	0.950
N1—C1	1.1500 (19)	C7—H72	0.950
C1—C2	1.423 (2)	C7—H73	0.950

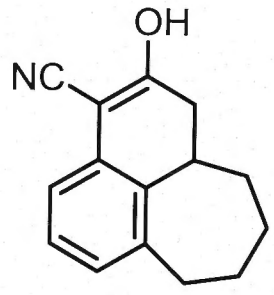
C2—C3	1.4827 (19)	C7—H74	0.950
C2—C14	1.3530 (19)	C8—C9	1.391 (2)
C3—C4	1.496 (2)	C8—C13	1.4035 (18)
C4—C5	1.542 (3)	C9—C10	1.379 (2)
C4—C51	1.592 (5)	C9—H91	0.950
C4—H41	0.950	C10—C11	1.382 (2)
C4—H42	0.950	C10—H101	0.950
C4—H43	0.950	C11—C12	1.3743 (19)
C4—H44	0.950	C11—H111	0.950
C5—C6	1.520 (4)	C12—C13	1.4067 (19)
C5—C14	1.558 (3)	C12—H121	0.950
C5—H51	0.950	C13—C14	1.4571 (19)
C6—C7	1.522 (3)	C14—C51	1.540 (5)
C6—H61	0.950	C51—C61	1.503 (9)
C6—H62	0.950	C51—H511	0.950
C7—C8	1.511 (2)	C61—H611	0.950
C7—C61	1.468 (6)	C61—H612	0.950
O1···C3^{i}	3.081 (2)	N1···C51^{iv}	3.561 (5)
O1···C4^{i}	3.277 (2)	C1···C13^{ii}	3.570 (2)
O1···O1^{i}	3.404 (2)	C1···C8^{ii}	3.580 (2)
O1···C5^{i}	3.423 (3)	C2···C12^{ii}	3.546 (2)
O1···C2^{i}	3.446 (2)	C3···C3^{i}	3.218 (3)
O1···C10^{ii}	3.577 (2)	C3···C11^{ii}	3.519 (2)
N1···C10^{iii}	3.484 (2)	C8···C61^{v}	3.484 (7)
N1···C8^{ii}	3.499 (2)	C9···C61^{v}	3.578 (7)
N1···C4^{iv}	3.506 (2)	C13···C61^{v}	3.568 (6)
N1—C1—C2	177.90 (15)	C61—C7—H73	108.9
C1—C2—C3	120.41 (12)	C8—C7—H74	108.9
C1—C2—C14	128.47 (13)	C61—C7—H74	108.9
C3—C2—C14	111.11 (13)	H73—C7—H74	109.5
C2—C3—O1	125.84 (15)	C7—C8—C9	119.64 (13)
C2—C3—C4	106.77 (12)	C7—C8—C13	121.72 (13)
O1—C3—C4	127.39 (14)	C9—C8—C13	118.64 (13)
C3—C4—C5	106.13 (13)	C8—C9—C10	121.53 (13)
C3—C4—C51	103.55 (18)	C8—C9—H91	119.2
C3—C4—H41	110.3	C10—C9—H91	119.2
C5—C4—H41	110.3	C9—C10—C11	120.04 (13)
C3—C4—H42	110.3	C9—C10—H101	120.0
C5—C4—H42	110.3	C11—C10—H101	120.0
H41—C4—H42	109.5	C10—C11—C12	119.65 (14)
C3—C4—H43	110.9	C10—C11—H111	120.2
C51—C4—H43	110.9	C12—C11—H111	120.2
C3—C4—H44	110.9	C11—C12—C13	121.16 (13)
C51—C4—H44	110.9	C11—C12—H121	119.4
H43—C4—H44	109.5	C13—C12—H121	119.4
C4—C5—C6	115.9 (2)	C12—C13—C8	118.98 (12)
C4—C5—C14	101.98 (17)	C12—C13—C14	122.19 (12)
C6—C5—C14	107.4 (2)	C8—C13—C14	118.83 (12)
C4—C5—H51	110.4	C5—C14—C13	118.61 (14)
C6—C5—H51	110.4	C5—C14—C2	109.64 (14)
C14—C5—H51	110.4	C13—C14—C2	131.33 (14)
C5—C6—C7	109.3 (2)	C13—C14—C51	116.1 (2)

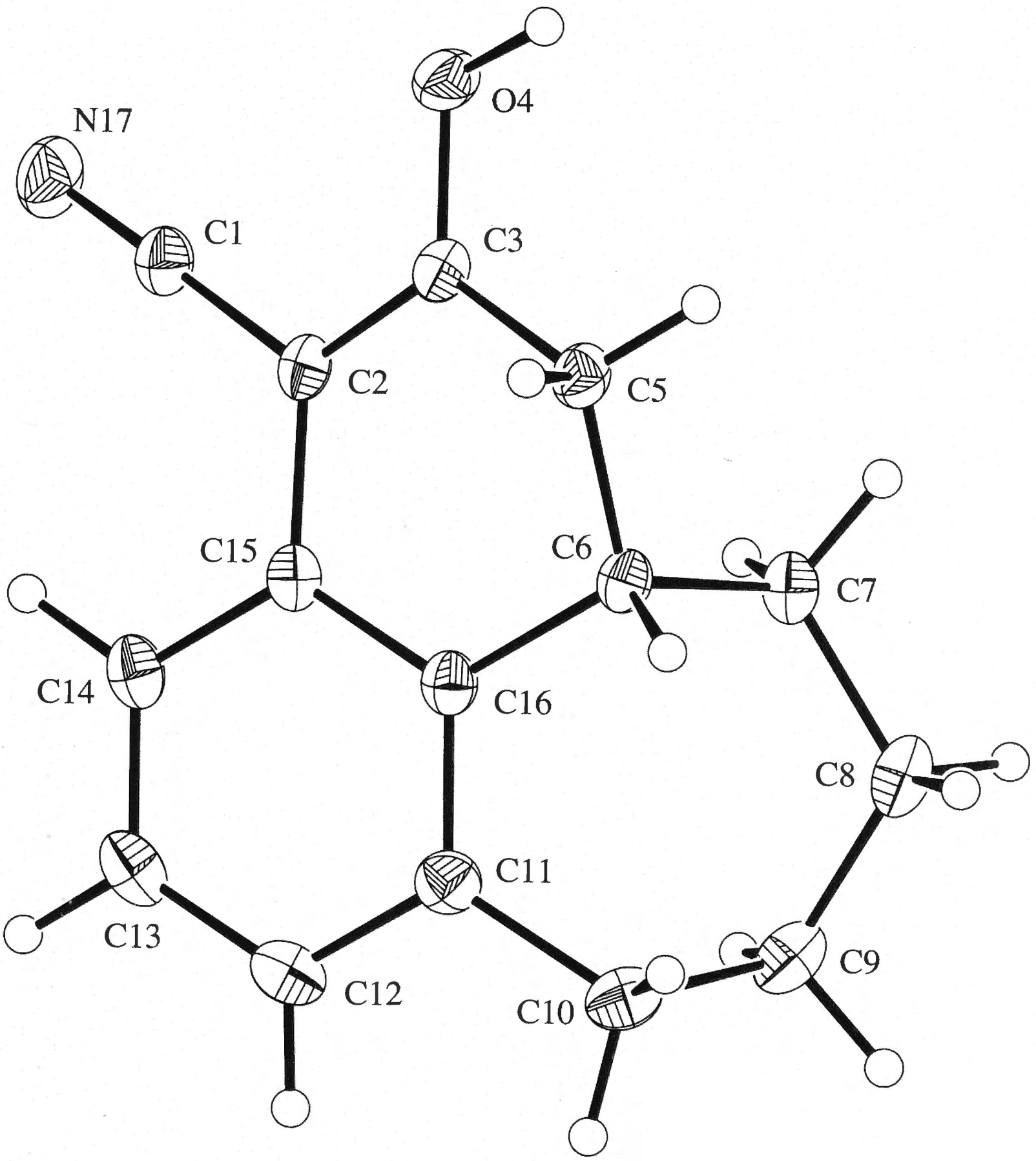
C5—C6—H61	109.5	C2—C14—C51	108.1 (2)
C7—C6—H61	109.5	C14—C51—C4	100.5 (3)
C5—C6—H62	109.5	C14—C51—C61	103.3 (5)
C7—C6—H62	109.5	C4—C51—C61	113.4 (5)
H61—C6—H62	109.5	C14—C51—H511	112.9
C6—C7—C8	114.10 (14)	C4—C51—H511	112.9
C8—C7—C61	111.6 (2)	C61—C51—H511	112.9
C6—C7—H71	108.3	C51—C61—C7	112.8 (5)
C8—C7—H71	108.3	C51—C61—H611	108.6
C6—C7—H72	108.3	C7—C61—H611	108.6
C8—C7—H72	108.3	C51—C61—H612	108.6
H71—C7—H72	109.5	C7—C61—H612	108.6
C8—C7—H73	108.9	H611—C61—H612	109.5
O1—C3—C2—C1	1.0 (2)	C4—C51—C61—C7	175.5 (3)
O1—C3—C2—C14	−178.4 (1)	C5—C6—C7—C8	50.3 (2)
O1—C3—C4—C5	165.9 (2)	C5—C14—C13—C8	−13.6 (2)
O1—C3—C4—C51	−162.1 (3)	C5—C14—C13—C12	166.6 (2)
C1—C2—C3—C4	−178.5 (1)	C6—C5—C14—C13	44.7 (2)
C1—C2—C14—C5	−168.0 (2)	C6—C7—C8—C9	161.3 (2)
C1—C2—C14—C13	4.3 (3)	C6—C7—C8—C13	−18.6 (2)
C1—C2—C14—C51	158.8 (3)	C7—C6—C5—C14	−61.3 (3)
C2—C3—C4—C5	−14.6 (2)	C7—C8—C9—C10	−179.7 (1)
C2—C3—C4—C51	17.4 (3)	C7—C8—C13—C12	179.4 (1)
C2—C14—C5—C4	−19.6 (2)	C7—C8—C13—C14	−0.4 (2)
C2—C14—C5—C6	−141.9 (2)	C7—C61—C51—C14	67.6 (5)
C2—C14—C13—C8	174.7 (1)	C8—C7—C61—C51	−49.6 (5)
C2—C14—C13—C12	−5.1 (2)	C8—C9—C10—C11	−0.1 (2)
C2—C14—C51—C4	31.1 (4)	C8—C13—C12—C11	0.7 (2)
C2—C14—C51—C61	148.4 (4)	C8—C13—C14—C51	21.8 (3)
C3—C2—C14—C5	11.4 (2)	C9—C8—C7—C61	−166.4 (3)
C3—C2—C14—C13	−176.4 (1)	C9—C8—C13—C12	−0.5 (2)
C3—C2—C14—C51	−21.9 (3)	C9—C8—C13—C14	179.7 (1)
C3—C4—C5—C6	136.4 (2)	C9—C10—C11—C12	0.3 (2)
C3—C4—C5—C14	20.1 (2)	C10—C9—C8—C13	0.2 (2)
C3—C4—C51—C14	−28.3 (3)	C10—C11—C12—C13	−0.6 (2)
C3—C4—C51—C61	−137.9 (4)	C11—C12—C13—C14	−179.5 (1)
C4—C3—C2—C14	2.2 (2)	C12—C13—C14—C51	−158.0 (3)
C4—C5—C6—C7	−174.5 (2)	C13—C8—C7—C61	13.7 (3)
C4—C5—C14—C13	167.0 (1)	C13—C14—C51—C61	−52.7 (5)
C4—C51—C14—C13	−170.0 (2)		

Symmetry codes: (i) $-x, -y+1, -z+1$; (ii) $-x+1, -y+1, -z+1$; (iii) $x-1/2, -y+3/2, z+1/2$; (iv) $x, y+1, z$; (v) $-x+1/2, y+1/2, -z+1/2$.

Appendix 9

X-ray Crystal Structure Report for Compound 4.97.





Crystal structure of $C_{15}H_{15}NO.H_2O$ — ban1118

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Abstract

The crystal structure of $C_{15}H_{15}NO.H_2O$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{15}H_{15}NO$ and one water molecule of crystallization.

Experimental

The compound was prepared by NH and crystallized from dichloromethane/diethylether in an open vessel. The sample ID is NH7-14-f2.

Refinement

All H atoms were located in a difference electron density map. Those bonded to O were included at these positions; those bonded to C were included at calculated positions. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C—H in the range 0.93–0.98, O—H = 0.82 Å) and with U_{iso}(H) in the range 1.2-1.5 times U_{eq} of the parent atom, after which the positions were refined without restraints and the displacement parameters were held fixed.

The largest peaks in the final difference electron density map are located midway along C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*-II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Mackay, S., Gilmore, C. J., Edwards, C., Stewart, N. & Shankland, K. (2000). *maXus* Computer Program for the Solution and Refinement of Crystal Structures. Nonius, The Netherlands, MacScience, Japan & The University of Glasgow.

Coppens, P. (1970). The Evaluation of Absorption and Extinction in Single-Crystal Structure Analysis. Crystallographic Computing. F. R. Ahmed, S. R. Hall and C. P. Huber, eds., Munksgaard. Copenhagen. pp 255-270.

Molecular Structure Corporation. (1992–1997). *TEXSAN*. Single Crystal Structure Analysis Software. Version 1.8. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Johnson, C. K. (1976). *ORTEP*II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.

(ban1118)

Crystal data

$C_{15}H_{15}NO{\cdot}H_2O$
$M_r = 243.31$
Monoclinic, $P2_1/n$
$a = 12.3070\ (2)$ Å
$b = 8.1121\ (1)$ Å
$c = 13.8164\ (3)$ Å
$\beta = 114.2477\ (10)°$
$V = 1257.68\ (4)$ Å^3
$Z = 4$

$F(000) = 520$
$D_x = 1.285$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 15317 reflections
$\theta = 2.6–27.5°$
$\mu = 0.09$ mm^{-1}
$T = 200$ K
Block, Colourless
$0.42 \times 0.35 \times 0.11$ mm

Data collection

Nonius KappaCCD diffractometer
graphite
φ and ω scans with CCD
Absorption correction: Integration via Gaussian method (Coppens, 1970) implemented in *maXus* (2000)
$T_{min} = 0.969$, $T_{max} = 0.991$
25780 measured reflections
2873 independent reflections

2438 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.043$
$\theta_{max} = 27.5°$, $\theta_{min} = 2.9°$
$h = -15 \rightarrow 15$
$k = -10 \rightarrow 9$
$l = -17 \rightarrow 17$

Refinement

Refinement on F^2

Least-squares matrix: Full

$R[F^2 > 2\sigma(F^2)] = 0.038$

$wR(F^2) = 0.102$

$S = 0.98$
2872 reflections
214 parameters
0 restraints

Primary atom site location: Structure-invariant direct methods
Hydrogen site location: Inferred from neighbouring sites
Only H-atom coordinates refined
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.06P)^2 + 0.27P]$,
where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.003$
$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.65897 (10)	0.60459 (13)	0.52225 (9)	0.0353
C2	0.62100 (9)	0.45900 (12)	0.45917 (8)	0.0308
C3	0.64262 (9)	0.31102 (12)	0.50884 (8)	0.0310
O4	0.70131 (8)	0.30323 (10)	0.61430 (6)	0.0400
C5	0.59523 (11)	0.15685 (13)	0.44666 (9)	0.0340
C6	0.58117 (9)	0.16480 (12)	0.33086 (8)	0.0302
C7	0.69600 (10)	0.11308 (14)	0.31969 (9)	0.0356
C8	0.67447 (12)	0.03981 (15)	0.21146 (11)	0.0426
C9	0.61100 (12)	0.14833 (16)	0.11456 (10)	0.0453
C10	0.48530 (11)	0.20501 (17)	0.09885 (10)	0.0446
C11	0.48994 (9)	0.34960 (14)	0.16915 (9)	0.0356
C12	0.45429 (11)	0.50514 (16)	0.12396 (10)	0.0431
C13	0.46860 (11)	0.64321 (15)	0.18658 (10)	0.0434
C14	0.52113 (10)	0.62869 (14)	0.29586 (10)	0.0372
C15	0.55743 (9)	0.47399 (12)	0.34320 (9)	0.0305
C16	0.53876 (9)	0.33239 (12)	0.27985 (8)	0.0301
N17	0.68799 (10)	0.72246 (13)	0.57216 (9)	0.0491
O18	0.69804 (8)	0.01433 (10)	0.69457 (7)	0.0425
H41	0.7018 (14)	0.188 (2)	0.6411 (13)	0.0620*
H51	0.6452 (11)	0.0629 (18)	0.4819 (11)	0.0421*
H52	0.5162 (11)	0.1347 (16)	0.4486 (10)	0.0412*
H61	0.5192 (11)	0.0833 (16)	0.2909 (10)	0.0361*
H71	0.7531 (12)	0.2093 (17)	0.3370 (10)	0.0417*
H72	0.7379 (12)	0.0271 (17)	0.3771 (11)	0.0435*
H81	0.7545 (14)	0.0054 (17)	0.2148 (12)	0.0526*
H82	0.6250 (13)	−0.0639 (19)	0.2030 (11)	0.0524*
H91	0.6628 (13)	0.249 (2)	0.1183 (12)	0.0537*
H92	0.6050 (13)	0.0823 (19)	0.0501 (12)	0.0554*
H101	0.4403 (13)	0.2411 (19)	0.0231 (12)	0.0528*
H102	0.4408 (13)	0.1111 (19)	0.1122 (11)	0.0523*
H121	0.4227 (14)	0.5156 (17)	0.0483 (13)	0.0512*
H131	0.4422 (13)	0.7507 (19)	0.1531 (12)	0.0530*
H141	0.5356 (12)	0.7282 (18)	0.3427 (11)	0.0451*
H181	0.7033 (14)	−0.077 (2)	0.6596 (13)	0.0659*
H182	0.7392 (16)	−0.002 (2)	0.7623 (16)	0.0659*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0373 (5)	0.0278 (5)	0.0411 (6)	0.0000 (4)	0.0164 (5)	−0.0022 (4)
C2	0.0343 (5)	0.0239 (5)	0.0371 (6)	−0.0009 (4)	0.0176 (4)	−0.0041 (4)
C3	0.0356 (5)	0.0277 (5)	0.0337 (5)	−0.0014 (4)	0.0182 (4)	−0.0034 (4)
O4	0.0573 (5)	0.0300 (4)	0.0319 (4)	−0.0020 (3)	0.0175 (4)	−0.0021 (3)
C5	0.0445 (6)	0.0238 (5)	0.0362 (6)	−0.0016 (4)	0.0191 (5)	−0.0016 (4)
C6	0.0328 (5)	0.0241 (5)	0.0346 (5)	−0.0025 (4)	0.0148 (4)	−0.0044 (4)
C7	0.0354 (5)	0.0284 (5)	0.0447 (6)	0.0020 (4)	0.0181 (5)	−0.0020 (4)
C8	0.0475 (7)	0.0344 (6)	0.0557 (7)	−0.0017 (5)	0.0312 (6)	−0.0091 (5)
C9	0.0549 (7)	0.0456 (7)	0.0428 (6)	−0.0061 (6)	0.0275 (6)	−0.0113 (5)
C10	0.0464 (7)	0.0484 (7)	0.0343 (6)	−0.0060 (5)	0.0119 (5)	−0.0086 (5)
C11	0.0299 (5)	0.0392 (6)	0.0353 (6)	−0.0019 (4)	0.0110 (4)	−0.0020 (4)
C12	0.0368 (6)	0.0481 (7)	0.0376 (6)	0.0018 (5)	0.0086 (5)	0.0076 (5)
C13	0.0379 (6)	0.0356 (6)	0.0512 (7)	0.0051 (5)	0.0127 (5)	0.0111 (5)
C14	0.0359 (6)	0.0272 (5)	0.0483 (6)	0.0020 (4)	0.0169 (5)	0.0018 (5)
C15	0.0286 (5)	0.0264 (5)	0.0383 (6)	0.0005 (4)	0.0156 (4)	−0.0009 (4)
C16	0.0267 (5)	0.0282 (5)	0.0362 (5)	−0.0005 (4)	0.0138 (4)	−0.0018 (4)
N17	0.0531 (6)	0.0323 (5)	0.0569 (7)	−0.0040 (4)	0.0174 (5)	−0.0124 (5)
O18	0.0604 (5)	0.0311 (4)	0.0330 (4)	0.0016 (4)	0.0162 (4)	0.0003 (3)

Geometric parameters (Å, º)

C1—C2	1.4277 (14)	C8—H82	1.016 (15)
C1—N17	1.1468 (15)	C9—C10	1.5414 (18)
C2—C3	1.3538 (14)	C9—H91	1.023 (16)
C2—C15	1.4713 (15)	C9—H92	1.016 (15)
C3—O4	1.3358 (13)	C10—C11	1.5090 (16)
C3—C5	1.4936 (14)	C10—H101	1.006 (15)
O4—H41	1.005 (17)	C10—H102	0.999 (15)
C5—C6	1.5384 (15)	C11—C12	1.3962 (16)
C5—H51	0.975 (14)	C11—C16	1.4017 (15)
C5—H52	1.000 (13)	C12—C13	1.3816 (18)
C6—C7	1.5415 (14)	C12—H121	0.958 (16)
C6—C16	1.5216 (14)	C13—C14	1.3820 (18)
C6—H61	0.989 (13)	C13—H131	0.978 (16)
C7—C8	1.5278 (16)	C14—C15	1.4007 (14)
C7—H71	1.011 (13)	C14—H141	1.004 (14)
C7—H72	1.023 (14)	C15—C16	1.4047 (14)
C8—C9	1.5227 (19)	O18—H181	0.903 (19)
C8—H81	1.006 (16)	O18—H182	0.87 (2)
O4···O18	2.600 (1)	O18···C5	3.333 (2)
O4···O18^{i}	2.959 (1)	O18···C3	3.377 (1)
O4···C14^{ii}	3.483 (2)	O18···N17^{v}	3.390 (1)
O4···C11^{iii}	3.538 (2)	N17···C13^{vi}	3.336 (2)
O4···C10^{iii}	3.589 (2)	N17···C5^{ii}	3.526 (2)
O18···N17^{iv}	2.883 (1)	C1···C2^{ii}	3.596 (2)

C2—C1—N17	179.07 (12)	C8—C9—C10	114.78 (10)
C1—C2—C3	118.50 (10)	C8—C9—H91	109.4 (9)
C1—C2—C15	119.40 (9)	C10—C9—H91	109.8 (9)
C3—C2—C15	122.09 (9)	C8—C9—H92	107.0 (9)
C2—C3—O4	120.04 (9)	C10—C9—H92	109.0 (8)
C2—C3—C5	120.13 (10)	H91—C9—H92	106.5 (12)
O4—C3—C5	119.75 (9)	C9—C10—C11	111.76 (10)
C3—O4—H41	111.4 (9)	C9—C10—H101	109.0 (8)
C3—C5—C6	114.43 (9)	C11—C10—H101	107.6 (9)
C3—C5—H51	110.5 (8)	C9—C10—H102	110.0 (8)
C6—C5—H51	109.3 (8)	C11—C10—H102	110.7 (8)
C3—C5—H52	106.8 (7)	H101—C10—H102	107.7 (12)
C6—C5—H52	109.9 (7)	C10—C11—C12	119.52 (11)
H51—C5—H52	105.5 (10)	C10—C11—C16	120.72 (10)
C5—C6—C7	112.12 (9)	C12—C11—C16	119.55 (10)
C5—C6—C16	112.95 (8)	C11—C12—C13	121.11 (11)
C7—C6—C16	110.55 (8)	C11—C12—H121	118.7 (8)
C5—C6—H61	106.5 (7)	C13—C12—H121	120.1 (8)
C7—C6—H61	106.9 (7)	C12—C13—C14	119.81 (11)
C16—C6—H61	107.5 (7)	C12—C13—H131	119.6 (9)
C6—C7—C8	113.97 (9)	C14—C13—H131	120.5 (9)
C6—C7—H71	110.1 (7)	C13—C14—C15	120.19 (11)
C8—C7—H71	110.8 (7)	C13—C14—H141	121.0 (8)
C6—C7—H72	107.4 (7)	C15—C14—H141	118.8 (8)
C8—C7—H72	108.8 (7)	C2—C15—C14	120.50 (9)
H71—C7—H72	105.3 (10)	C2—C15—C16	119.26 (9)
C7—C8—C9	117.12 (10)	C14—C15—C16	120.17 (10)
C7—C8—H81	106.9 (9)	C6—C16—C15	120.32 (9)
C9—C8—H81	109.8 (9)	C6—C16—C11	120.41 (9)
C7—C8—H82	106.8 (8)	C15—C16—C11	119.05 (9)
C9—C8—H82	108.1 (8)	H181—O18—H182	108.3 (15)
H81—C8—H82	107.7 (11)		

O4—C3—C2—C1	−1.9 (2)	C6—C16—C11—C10	−3.7 (2)
O4—C3—C2—C15	179.6 (1)	C6—C16—C11—C12	−178.4 (1)
O4—C3—C5—C6	−154.0 (1)	C6—C16—C15—C14	178.3 (1)
C1—C2—C3—C5	174.8 (1)	C7—C6—C16—C11	71.2 (1)
C1—C2—C15—C14	−8.0 (2)	C7—C6—C16—C15	−103.3 (1)
C1—C2—C15—C16	168.8 (1)	C7—C8—C9—C10	−59.6 (2)
C2—C3—C5—C6	29.3 (2)	C8—C7—C6—C16	−80.8 (1)
C2—C15—C14—C13	175.7 (1)	C8—C9—C10—C11	80.3 (1)
C2—C15—C16—C6	1.5 (2)	C9—C10—C11—C12	109.0 (1)
C2—C15—C16—C11	−173.1 (1)	C9—C10—C11—C16	−65.7 (2)
C3—C2—C15—C14	170.5 (1)	C10—C11—C12—C13	−173.4 (1)
C3—C2—C15—C16	−12.7 (2)	C10—C11—C16—C15	170.8 (1)
C3—C5—C6—C7	88.1 (1)	C11—C12—C13—C14	1.3 (2)
C3—C5—C6—C16	−37.6 (1)	C11—C16—C15—C14	3.7 (2)
C5—C3—C2—C15	−3.7 (2)	C12—C11—C16—C15	−3.8 (2)
C5—C6—C7—C8	152.2 (1)	C12—C13—C14—C15	−1.4 (2)
C5—C6—C16—C11	−162.2 (1)	C13—C12—C11—C16	1.4 (2)
C5—C6—C16—C15	23.3 (2)	C13—C14—C15—C16	−1.1 (2)
C6—C7—C8—C9	59.3 (2)		

Symmetry codes: (i) −*x*+3/2, *y*+1/2, −*z*+3/2; (ii) −*x*+1, −*y*+1, −*z*+1; (iii) *x*+1/2, −*y*+1/2, *z*+1/2; (iv) *x*, *y*−1, *z*; (v) −*x*+3/2, *y*−1/2, −*z*+3/2; (vi) *x*+1/2, −*y*+3/2, *z*+1/2.

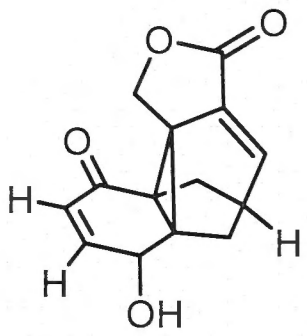
Hydrogen-bond geometry (Å, º)

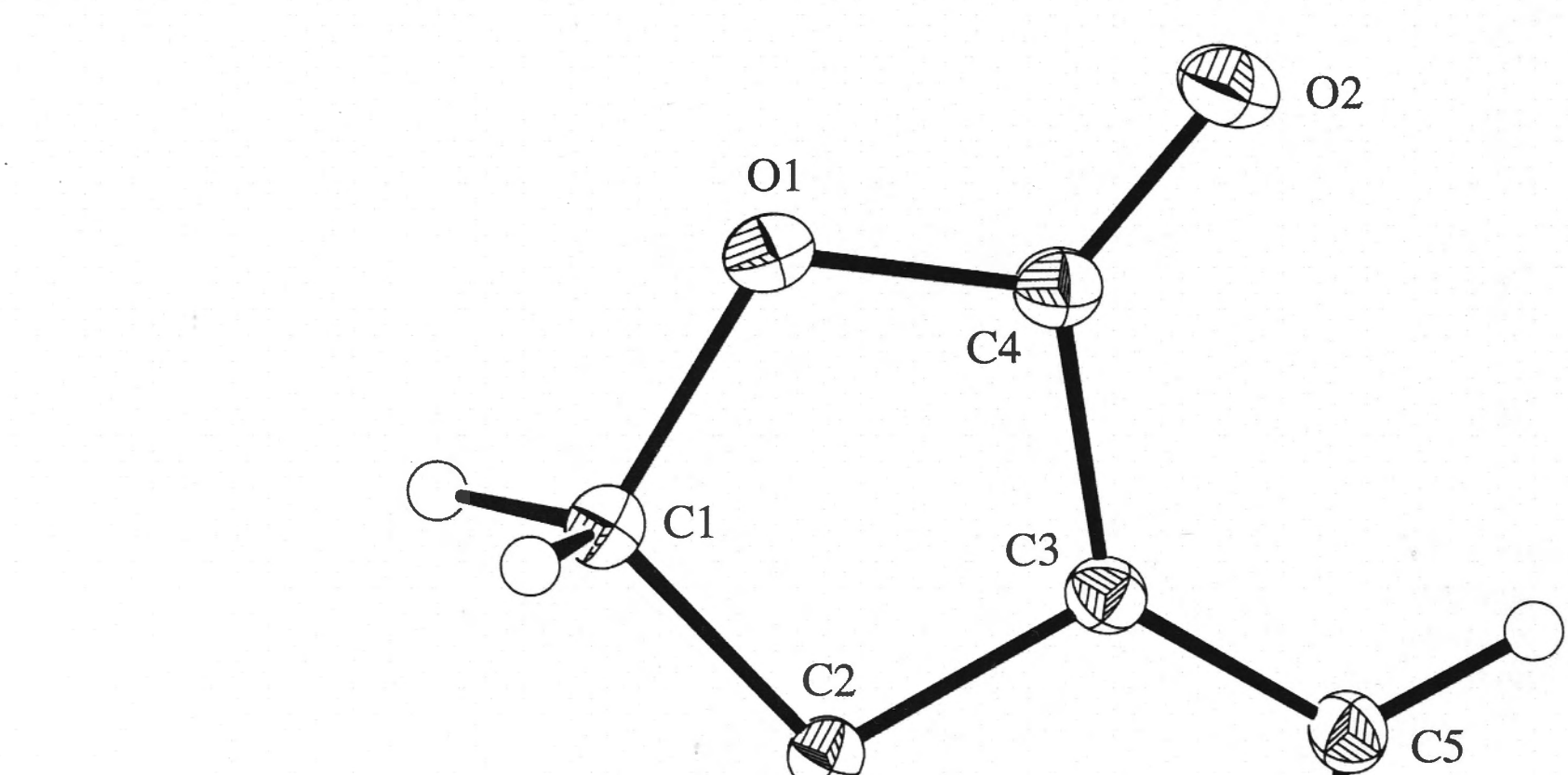
D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H41···O18	1.005 (17)	1.600 (17)	2.6001 (17)	172.9 (15)
O18—H181···N17^{iv}	0.903 (19)	1.987 (19)	2.8826 (17)	171.3 (15)
O18—H182···O4^{v}	0.87 (2)	2.218 (18)	2.9586 (17)	142.7 (15)

Symmetry codes: (iv) *x*, *y*−1, *z*; (v) −*x*+3/2, *y*−1/2, −*z*+3/2.

Appendix 10

X-ray Crystal Structure Report for Compound 5.10.





Crystal structure of $C_{14}H_{12}O_4$ — ban1236

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Abstract

The crystal structure of $C_{14}H_{12}O_4$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{14}H_{12}O_4$.

Experimental

The compound was prepared by NH and crystallized from deuterochloroform. The sample ID is NH10-71-3-f2.

Refinement

All H atoms were located in a difference electron-density map and those bonded to C were included at calculated positions. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C—H in the range 0.93–0.98Å, O—H = 0.82Å) and with U_{iso}(H) in the range 1.2-1.5 times U_{eq} of the parent atom, after which the positions were refined freely and the displacement parameters were held fixed.

Most of the largest peaks in the final difference electron density map are located midway along C—C bonds.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP*-II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Mackay, S., Gilmore, C. J., Edwards, C., Stewart, N. & Shankland, K. (2000). *maXus* Computer Program for the Solution and Refinement of Crystal Structures. Nonius, The Netherlands, MacScience, Japan & The University of Glasgow.

Coppens, P. (1970). The Evaluation of Absorption and Extinction in Single-Crystal Structure Analysis. Crystallographic Computing. F. R. Ahmed, S. R. Hall and C. P. Huber, eds., Munksgaard. Copenhagen. pp 255-270.

Molecular Structure Corporation. (1992–1997). *TEXSAN*. Single Crystal Structure Analysis Software. Version 1.8. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Johnson, C. K. (1976). *ORTEP*II, A Fortran Thermal-Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.

Larson, A. C. (1970). Crystallographic Computing, Ed Ahmed, F.R., Munksgaard, Copenhagen, 291-294.

(ban1236)

Crystal data

$C_{14}H_{12}O_4$
$M_r = 244.25$
Monoclinic, $P2_1/c$
$a = 8.4024$ (2) Å
$b = 11.5575$ (2) Å
$c = 11.0597$ (2) Å
$\beta = 100.0908$ (12)°
$V = 1057.40$ (4) Å^3
$Z = 4$
$F(000) = 512$
$D_x = 1.534$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 11827 reflections
$\theta = 2.6$–27.5°
$\mu = 0.11$ mm^{-1}
$T = 200$ K
Block, Colourless
0.48 × 0.20 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
φ and ω scans with CCD
Absorption correction: Integration via Gaussian method (Coppens, 1970) implemented in *maXus* (2000)
$T_{min} = 0.963$, $T_{max} = 0.988$
21142 measured reflections
2425 independent reflections
2079 reflections with $I > 2.0\sigma(I)$
$R_{int} = 0.033$
$\theta_{max} = 27.5°$, $\theta_{min} = 2.6°$
$h = -10 \rightarrow 10$
$k = -14 \rightarrow 13$
$l = -14 \rightarrow 14$

Refinement

Refinement on F^2
Least-squares matrix: Full
$R[F^2 > 2\sigma(F^2)] = 0.034$
$wR(F^2) = 0.089$
$S = 0.96$
2425 reflections
200 parameters
0 restraints
Primary atom site location: Structure-invariant direct methods
Hydrogen site location: Inferred from neighbouring sites
Only H-atom coordinates refined
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.05P)^2 + 0.39P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.25$ e Å^{-3}
Extinction correction: Larson (1970), Equation 22
Extinction coefficient: 200 (30)

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.78793 (11)	0.60390 (8)	0.52159 (8)	0.0293
O2	1.02976 (11)	0.69068 (8)	0.54008 (8)	0.0336
O3	0.41874 (11)	0.61840 (8)	0.08061 (8)	0.0312
O4	0.63421 (11)	0.24838 (7)	0.14386 (9)	0.0292
C1	0.67753 (15)	0.53649 (11)	0.43201 (11)	0.0261
C2	0.75644 (13)	0.53099 (9)	0.31807 (10)	0.0209
C3	0.91011 (14)	0.59371 (10)	0.35164 (10)	0.0226
C4	0.92339 (14)	0.63622 (10)	0.47786 (11)	0.0250
C5	1.01035 (14)	0.60510 (10)	0.27137 (11)	0.0246
C6	0.94618 (15)	0.54988 (10)	0.14974 (11)	0.0250
C7	0.90338 (14)	0.42160 (10)	0.17296 (11)	0.0237
C8	0.75109 (13)	0.43183 (9)	0.22882 (10)	0.0208
C9	0.64636 (14)	0.32841 (10)	0.24430 (11)	0.0238

C10	0.47739 (14)	0.36361 (11)	0.25834 (12)	0.0281
C11	0.40868 (15)	0.46395 (11)	0.21809 (12)	0.0286
C12	0.49464 (14)	0.55055 (10)	0.15511 (11)	0.0242
C13	0.67139 (14)	0.54651 (10)	0.18156 (10)	0.0221
C14	0.77752 (15)	0.60420 (11)	0.10254 (11)	0.0254
H11	0.6686 (18)	0.4595 (13)	0.4709 (13)	0.0300*
H12	0.5724 (19)	0.5756 (13)	0.4212 (13)	0.0316*
H41	0.604 (2)	0.2901 (16)	0.0734 (16)	0.0449*
H51	1.1116 (18)	0.6468 (13)	0.2911 (13)	0.0295*
H61	1.0224 (17)	0.5581 (13)	0.0899 (13)	0.0282*
H71	0.9912 (18)	0.3820 (13)	0.2290 (13)	0.0293*
H72	0.8769 (17)	0.3785 (13)	0.0958 (14)	0.0290*
H91	0.6973 (18)	0.2832 (13)	0.3173 (13)	0.0281*
H101	0.4155 (19)	0.3048 (13)	0.2947 (14)	0.0348*
H111	0.2955 (19)	0.4805 (14)	0.2226 (14)	0.0349*
H141	0.7386 (17)	0.5840 (13)	0.0139 (14)	0.0301*
H142	0.7783 (18)	0.6890 (13)	0.1099 (13)	0.0300*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0319 (5)	0.0331 (5)	0.0237 (4)	−0.0014 (4)	0.0074 (3)	−0.0047 (3)
O2	0.0343 (5)	0.0350 (5)	0.0290 (5)	−0.0036 (4)	−0.0010 (4)	−0.0064 (4)
O3	0.0330 (5)	0.0275 (5)	0.0305 (5)	0.0071 (4)	−0.0015 (4)	0.0007 (4)
O4	0.0326 (5)	0.0203 (4)	0.0337 (5)	−0.0023 (3)	0.0033 (4)	−0.0031 (4)
C1	0.0256 (6)	0.0282 (6)	0.0255 (6)	−0.0010 (5)	0.0074 (5)	−0.0014 (5)
C2	0.0216 (5)	0.0199 (5)	0.0216 (5)	0.0007 (4)	0.0042 (4)	0.0005 (4)
C3	0.0236 (5)	0.0198 (5)	0.0239 (6)	0.0002 (4)	0.0030 (4)	−0.0009 (4)
C4	0.0271 (6)	0.0225 (6)	0.0249 (6)	0.0029 (4)	0.0032 (4)	−0.0004 (4)
C5	0.0238 (6)	0.0213 (6)	0.0291 (6)	−0.0025 (4)	0.0060 (5)	−0.0016 (4)
C6	0.0263 (6)	0.0250 (6)	0.0251 (6)	−0.0037 (4)	0.0086 (5)	−0.0013 (4)
C7	0.0238 (6)	0.0228 (6)	0.0256 (6)	−0.0008 (4)	0.0075 (5)	−0.0030 (5)
C8	0.0211 (5)	0.0191 (5)	0.0223 (5)	−0.0003 (4)	0.0038 (4)	0.0005 (4)
C9	0.0240 (6)	0.0196 (5)	0.0276 (6)	−0.0013 (4)	0.0042 (4)	0.0018 (4)
C10	0.0243 (6)	0.0273 (6)	0.0333 (6)	−0.0048 (5)	0.0069 (5)	0.0015 (5)
C11	0.0212 (6)	0.0308 (6)	0.0338 (7)	−0.0007 (5)	0.0044 (5)	−0.0019 (5)
C12	0.0260 (6)	0.0212 (5)	0.0244 (6)	0.0023 (4)	0.0016 (4)	−0.0037 (4)
C13	0.0244 (6)	0.0194 (5)	0.0223 (5)	−0.0005 (4)	0.0033 (4)	0.0011 (4)
C14	0.0302 (6)	0.0226 (6)	0.0238 (6)	−0.0026 (5)	0.0057 (5)	0.0023 (4)

Geometric parameters (Å, º)

O1—C1	1.4584 (15)	C6—C14	1.5543 (17)
O1—C4	1.3644 (15)	C6—H61	1.003 (14)
O2—C4	1.2054 (15)	C7—C8	1.5200 (15)
O3—C12	1.2314 (14)	C7—H71	0.989 (15)
O4—C9	1.4353 (14)	C7—H72	0.980 (15)
O4—H41	0.914 (18)	C8—C9	1.5116 (15)
C1—C2	1.5246 (15)	C8—C13	1.5348 (15)
C1—H11	0.996 (15)	C9—C10	1.5108 (16)
C1—H12	0.981 (16)	C9—H91	0.994 (15)
C2—C3	1.4706 (16)	C10—C11	1.3365 (18)
C2—C8	1.5080 (15)	C10—H101	0.984 (16)
C2—C13	1.5634 (15)	C11—C12	1.4782 (17)

C3—C4	1.4656 (16)	C11—H111	0.980 (16)
C3—C5	1.3329 (16)	C12—C13	1.4632 (16)
C5—C6	1.5012 (16)	C13—C14	1.5089 (16)
C5—H51	0.969 (15)	C14—H141	1.005 (15)
C6—C7	1.5574 (16)	C14—H142	0.984 (15)
O1···C14^{i}	3.495 (2)	O3···C9^{v}	3.211 (2)
O1···C3^{ii}	3.517 (1)	O3···C10^{v}	3.379 (2)
O1···C5^{ii}	3.548 (1)	O3···C12^{iv}	3.436 (2)
O1···C10^{iii}	3.597 (2)	O3···C13^{iv}	3.441 (1)
O2···C8^{ii}	3.206 (1)	O3···O4^{v}	3.495 (1)
O2···C9^{ii}	3.296 (1)	O3···C14^{iv}	3.503 (2)
O2···C14^{i}	3.332 (2)	O3···C8^{iv}	3.518 (1)
O2···C6^{i}	3.355 (2)	O3···C7^{iv}	3.570 (1)
O2···C2^{ii}	3.356 (1)	O3···C9^{iv}	3.592 (2)
O2···C7^{ii}	3.383 (2)	O4···C5^{vi}	3.400 (1)
O2···C3^{ii}	3.504 (2)	O4···C12^{vii}	3.491 (2)
O2···C5^{i}	3.505 (2)	O4···C1^{vii}	3.577 (2)
O2···C1^{ii}	3.574 (2)	C3···C4^{ii}	3.413 (2)
O3···O4^{iv}	2.889 (1)	C4···C4^{ii}	3.405 (2)
C1—O1—C4	112.10 (9)	H71—C7—H72	110.0 (12)
C9—O4—H41	106.9 (11)	C7—C8—C2	113.24 (9)
O1—C1—C2	105.48 (9)	C7—C8—C9	122.19 (10)
O1—C1—H11	105.7 (8)	C2—C8—C9	118.55 (9)
C2—C1—H11	113.3 (8)	C7—C8—C13	106.07 (9)
O1—C1—H12	106.8 (9)	C2—C8—C13	61.83 (7)
C2—C1—H12	115.6 (9)	C9—C8—C13	119.57 (9)
H11—C1—H12	109.2 (12)	C8—C9—O4	112.70 (9)
C1—C2—C3	105.10 (9)	C8—C9—C10	112.02 (10)
C1—C2—C8	127.25 (10)	O4—C9—C10	108.20 (9)
C3—C2—C8	117.64 (9)	C8—C9—H91	109.4 (8)
C1—C2—C13	127.02 (10)	O4—C9—H91	104.6 (8)
C3—C2—C13	114.82 (9)	C10—C9—H91	109.7 (8)
C8—C2—C13	59.93 (7)	C9—C10—C11	123.94 (11)
C2—C3—C4	108.82 (10)	C9—C10—H101	115.4 (9)
C2—C3—C5	120.66 (11)	C11—C10—H101	120.5 (9)
C4—C3—C5	130.52 (11)	C10—C11—C12	121.75 (11)
C3—C4—O1	108.47 (10)	C10—C11—H111	121.2 (9)
C3—C4—O2	130.08 (11)	C12—C11—H111	116.8 (9)
O1—C4—O2	121.45 (11)	C11—C12—O3	120.53 (11)
C3—C5—C6	112.65 (10)	C11—C12—C13	116.54 (10)
C3—C5—H51	122.1 (9)	O3—C12—C13	122.86 (11)
C6—C5—H51	125.2 (9)	C8—C13—C2	58.24 (7)
C5—C6—C7	108.30 (10)	C8—C13—C12	117.56 (10)
C5—C6—C14	107.00 (10)	C2—C13—C12	118.22 (10)
C7—C6—C14	102.51 (9)	C8—C13—C14	108.18 (9)
C5—C6—H61	112.4 (8)	C2—C13—C14	113.17 (9)
C7—C6—H61	113.0 (8)	C12—C13—C14	123.52 (10)
C14—C6—H61	113.0 (8)	C6—C14—C13	102.92 (9)
C6—C7—C8	103.19 (9)	C6—C14—H141	110.8 (8)
C6—C7—H71	112.1 (9)	C13—C14—H141	109.8 (8)
C8—C7—H71	111.7 (9)	C6—C14—H142	112.5 (9)
C6—C7—H72	111.4 (9)	C13—C14—H142	112.8 (9)

C8—C7—H72	108.3 (8)	H141—C14—H142	108.0 (12)
O1—C1—C2—C3	1.4 (1)	C3—C2—C8—C9	145.6 (1)
O1—C1—C2—C8	145.4 (1)	C3—C2—C8—C13	−104.1 (1)
O1—C1—C2—C13	−137.0 (1)	C3—C2—C13—C8	108.8 (1)
O1—C4—C3—C2	−0.4 (1)	C3—C2—C13—C12	−144.6 (1)
O1—C4—C3—C5	178.9 (1)	C3—C2—C13—C14	11.1 (1)
O2—C4—O1—C1	−178.6 (1)	C3—C5—C6—C7	−53.9 (1)
O2—C4—C3—C2	179.6 (1)	C3—C5—C6—C14	55.9 (1)
O2—C4—C3—C5	−1.1 (2)	C4—C3—C2—C8	−148.8 (1)
O3—C12—C11—C10	152.7 (1)	C4—C3—C2—C13	143.6 (1)
O3—C12—C13—C2	138.9 (1)	C4—C3—C5—C6	−178.4 (1)
O3—C12—C13—C8	−154.2 (1)	C5—C3—C2—C8	31.8 (2)
O3—C12—C13—C14	−14.1 (2)	C5—C3—C2—C13	−35.8 (2)
O4—C9—C8—C2	171.66 (9)	C5—C6—C7—C8	72.8 (1)
O4—C9—C8—C7	−37.5 (1)	C5—C6—C14—C13	−75.0 (1)
O4—C9—C8—C13	99.7 (1)	C6—C7—C8—C9	167.90 (9)
O4—C9—C10—C11	−101.6 (1)	C6—C7—C8—C13	25.9 (1)
C1—O1—C4—C3	1.4 (1)	C6—C14—C13—C8	−23.3 (1)
C1—C2—C3—C4	−0.7 (1)	C6—C14—C13—C12	−166.6 (1)
C1—C2—C3—C5	179.9 (1)	C7—C6—C14—C13	38.8 (1)
C1—C2—C8—C7	−147.9 (1)	C7—C8—C2—C13	96.4 (1)
C1—C2—C8—C9	5.5 (2)	C7—C8—C9—C10	−159.8 (1)
C1—C2—C8—C13	115.7 (1)	C7—C8—C13—C12	144.1 (1)
C1—C2—C13—C8	−116.1 (1)	C7—C8—C13—C14	−1.7 (1)
C1—C2—C13—C12	−9.5 (2)	C8—C2—C13—C12	106.6 (1)
C1—C2—C13—C14	146.2 (1)	C8—C2—C13—C14	−97.7 (1)
C2—C1—O1—C4	−1.8 (1)	C8—C7—C6—C14	−40.1 (1)
C2—C3—C5—C6	0.8 (2)	C8—C9—C10—C11	23.2 (2)
C2—C8—C7—C6	−39.9 (1)	C8—C13—C12—C11	22.7 (2)
C2—C8—C9—C10	49.4 (1)	C9—C8—C2—C13	−110.2 (1)
C2—C8—C13—C12	−107.7 (1)	C9—C8—C13—C12	0.9 (2)
C2—C8—C13—C14	106.5 (1)	C9—C8—C13—C14	−144.9 (1)
C2—C13—C8—C7	−108.14 (9)	C9—C10—C11—C12	0.0 (2)
C2—C13—C8—C9	108.6 (1)	C10—C9—C8—C13	−22.6 (1)
C2—C13—C12—C11	−44.1 (1)	C10—C11—C12—C13	−24.3 (2)
C2—C13—C14—C6	39.2 (1)	C11—C12—C13—C14	162.8 (1)
C3—C2—C8—C7	−7.7 (1)		

Symmetry codes: (i) *x*, −*y*+3/2, *z*+1/2; (ii) −*x*+2, −*y*+1, −*z*+1; (iii) −*x*+1, −*y*+1, −*z*+1; (iv) −*x*+1, −*y*+1, −*z*; (v) −*x*+1, *y*+1/2, −*z*+1/2; (vi) −*x*+2, *y*−1/2, −*z*+1/2; (vii) −*x*+1, *y*−1/2, −*z*+1/2.

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H41···O3^{iv}	0.914 (18)	1.986 (19)	2.8887 (17)	169.4 (15)

Symmetry code: (iv) −*x*+1, −*y*+1, −*z*.

Appendix 11

Publications

(1)

"Probing for the Pharmacophore of the Cytotoxic Neoclerodane Salvileucalin B."

Nora Heinrich, Martin G. Banwell, Anthony C. Willis, Ian A. Cade, Robert J. Capon and Xiao-Cong Huang *The Australian Journal of Chemistry*, **2012**, *65*, 1679-1686.

(2)

"Reversible Cyclopropane Ring-Cleavage Reactions within Etheno-Bridged [4.3.1]Propelladiene Frameworks Leading to Aza- and Oxa-[5.6.5.6]fenestratetraenes."

Nora Heinrich, Anthony C. Willis, Ian A. Cade, Junming Ho, Michelle L. Coote and Martin G. Banwell *Chemistry—A European Journal*, **2012**, *18*, 13585-13588.

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Aust. J. Chem. **2012**, *65*, 1679–1686
http://dx.doi.org/10.1071/CH12358

Full Paper

Probing for the Pharmacophore of the Cytotoxic Neoclerodane Salvileucalin B

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The novel [4.3.1]propelladiene **2**, which embodies the key structural elements of the pentacyclic core of the cytotoxic neoclerodane salvileucalin B (**1**), has been prepared using a rhodium-catalysed intramolecular Büchner reaction as the key step. Compound **2** and the readily obtained derivatives **12**–**17** all proved to be essentially inactive when tested against a panel of four human cancer cell lines. Furthermore, not one of these compounds was a P-gp inhibitor.

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Introduction

In 2008 Takeya et al. reported[1] the isolation of salvileucalin B (**1**, Fig. 1), a neoclerodane, from the aerial parts of *Salvia leucantha* (Mexican bush sage) of the subgenus *Calosphace* (Labiatae). Its structure, including absolute configuration, was established through a combination of spectroscopic techniques including X-ray analysis and vibrational circular dichroism. The structurally novel propellane core associated with natural product **1** is believed to be formed by an intramolecular Diels–Alder reaction of the triene moiety associated with the co-occurring spirocyclic neoclerodane salvileucalin A, a proposal that is supported by very recent synthetic studies.[2] Compound **1** was shown to exert cytotoxic activity against the A549 and HT-29 human adenocarcinoma cell lines with half maximal inhibitory concentration (IC_{50}) values of 15.7 and 5.6 μM, respectively.[1] Arguably, these effects can be attributed to the presence of the α-alkylidene-γ-butyrolactone-type moiety embedded within the polycyclic framework.[3]

Accordingly, we speculated that the basic pharmacophore[4] associated with salvileucalin B is embodied within substructure **2** and that this, as well as related systems, could display similar activities to the natural product. Herein, therefore, we report the syntheses of compound **2** and various of its reduced forms together with the outcomes of the preliminary biological screening of this suite of salvileucalin B analogues.

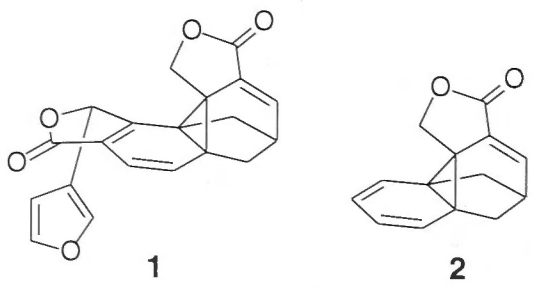


Fig. 1. Structures of salvileucalin B (**1**) and key substructure **2**.

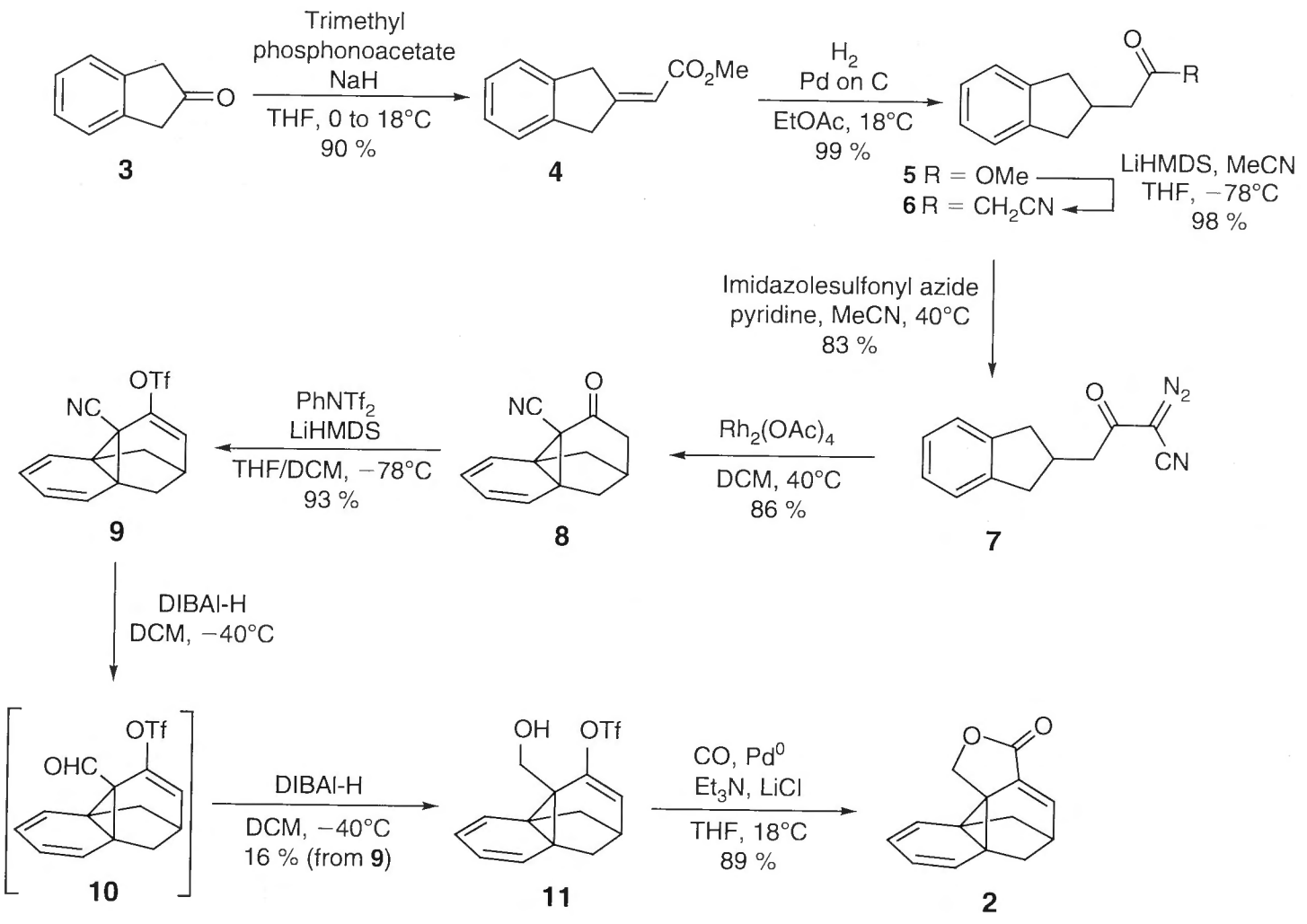
Results and Discussion

Synthetic Studies

The synthetic sequence used to prepare compound **2** is shown in Scheme 1. The key step employed in preparing the associated propellane framework was an intramolecular Büchner reaction,[5] a process used to great effect by Reisman et al. in their recently completed total synthesis of the natural product.[6] Thus, commercially available indane-2-one (**3**) was subjected to a Horner–Wadsworth–Emmons (HWE) reaction with the anion derived from trimethyl phosphonoacetate and the resulting α,β-unsaturated ester **4** (90 %)[7] then hydrogenated to give the corresponding saturated system **5** (99 %).[7] Treatment of compound **5** with the acetonitrile anion[8] afforded the β-ketonitrile **6** (98 %) that engaged in a diazotransfer reaction upon treatment with imidazolesulfonyl azide[9] and pyridine. Exposure of the resulting α-diazoketone **7** (83 %) to dirhodium tetraacetate in refluxing dichloromethane (DCM) afforded the Büchner product **8** (86 %),[†] the structure of which was established by a single-crystal X-ray analysis (see Experimental section and Supplementary Material for details).

While ketone **8** was readily converted into the corresponding enol triflate **9** (93 %) by treating the former compound with LiHMDS in the presence of *N*-phenyltriflimide ($PhNTf_2$), the next stage of the reaction sequence proved rather problematic. In

[†]When the Büchner reaction was effected using copper-based catalysts only small quantities of compound **8** were obtained.



Scheme 1. Synthesis of the core, **2**, of salvileucalin B (**1**).

particular, attempts to effect reduction of the nitrile **9**, via the corresponding aldehyde **10**, to the primary alcohol **11** were complicated by the tendency of the intermediate aldehyde to engage in an apparently reversible rearrangement reaction involving the norcaradiene unit.[‡] As a consequence, only a 16 % yield of compound **11** could be realised when using DIBAl-H as the reducing agent. Nevertheless, sufficient material could be accumulated by such means to allow the completion of the synthesis of target **2**. Thus, reaction of alcohol **11** with carbon monoxide in the presence of Pd^0, triethylamine, and lithium chloride at 18°C afforded the lactone **2** in 89 % yield. All the derived spectroscopic data were in accord with the assigned structure but final confirmation of this followed from a single-crystal X-ray analysis. The associated ORTEP diagram is shown in Fig. 2 and further details are provided in the Experimental section.

The generation of a series of partially reduced forms of compound **2** was readily achieved by exposing it to hydrogen in the presence of various catalysts (see Scheme 2 and Table 1), and by such means the polyhydro-forms **12**–**17** of compound **2** were produced. The structures of these were secured by conducting the usual range of spectroscopic analyses, and that of **17** (wherein the cyclopropane ring associated with precursor **2** had been hydrogenolysed) was confirmed by single-crystal X-ray analysis (see Experimental section for details).[10]

Interestingly, a related pair of partially reduced compounds and a cyclopropane ring-cleavage product were observed when the ester **18** derived from triflate **9** was exposed to hydrogen in the presence of Raney-cobalt (Scheme 3). In particular, a chromatographically separable mixture of compounds **19** (37 %), **20** (25 %), and **21** (5 %) was obtained and the structure of the last of these was secured by single-crystal X-ray analysis (see Experimental section for details).[10]

[‡]The details of this process will be the subject of a separate report.

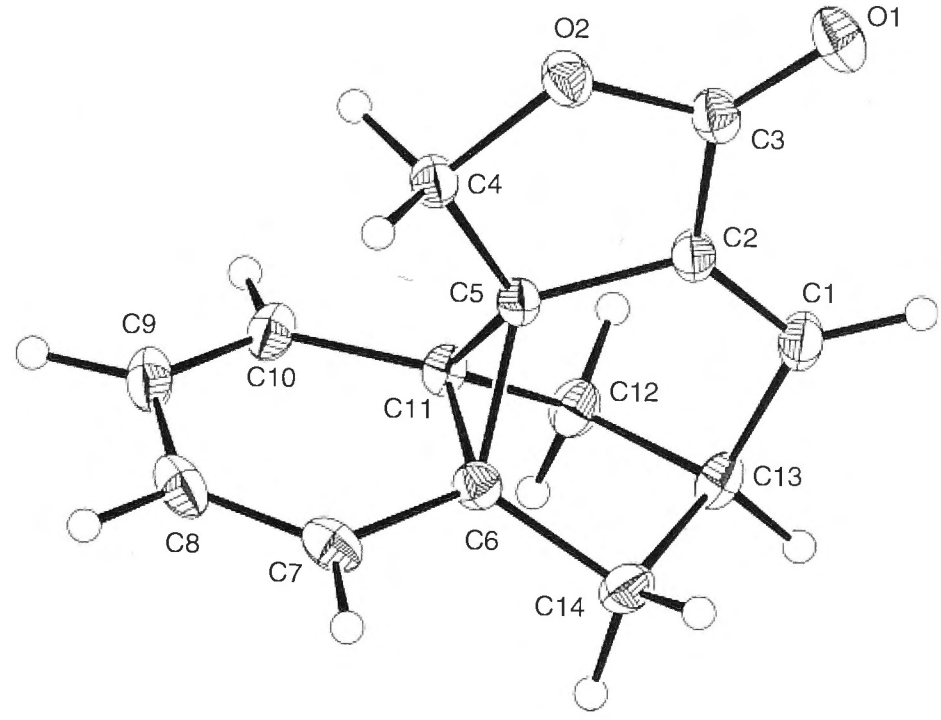
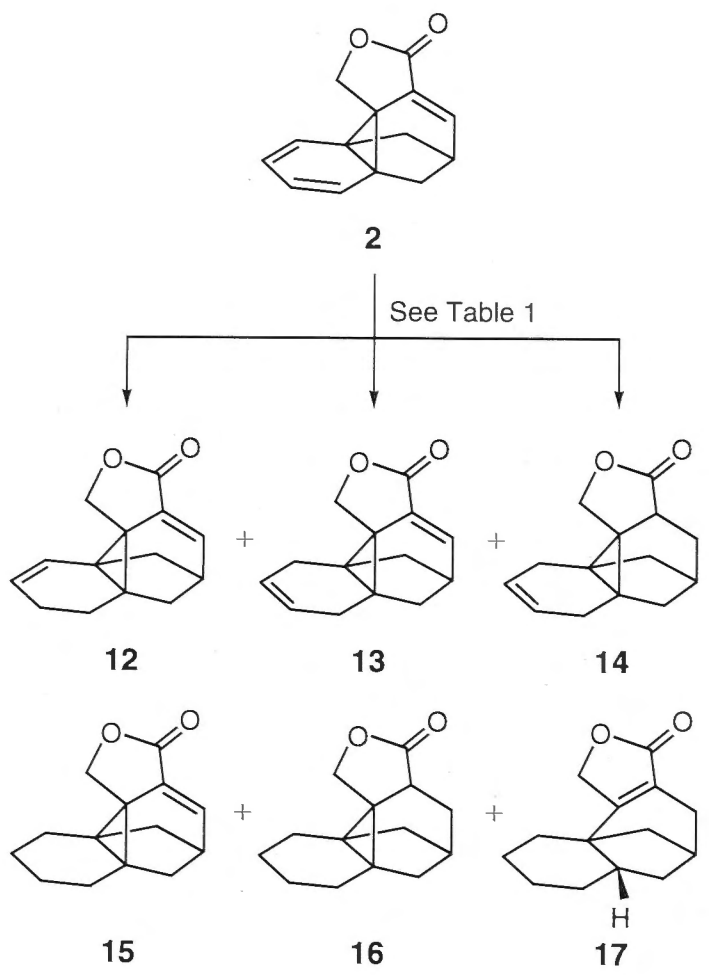


Fig. 2. ORTEP derived from the single-crystal X-ray analysis of compound **2**. Anisotropic displacement ellipsoids display 30 % probability levels. Hydrogen atoms are drawn as circles with small radii.

Biological Evaluation of Compounds 2 and 12–17

Compounds **2** and **12**–**17** were tested against the cell lines SW620, SW620 Ad300, KB-3-1, and KB-V1 which are, respectively, a human colon cancer cell line, a daughter cell line overexpressing P-gp (prepared by culturing SW620 in the presence of adriamycin), a human cervical cancer cell line, and a daughter cell line overexpressing P-gp (prepared by culturing KB-3-1 in the presence of vinblastine). P-gp is an ATP binding cassette (ABC) transporter protein that drives multi-drug

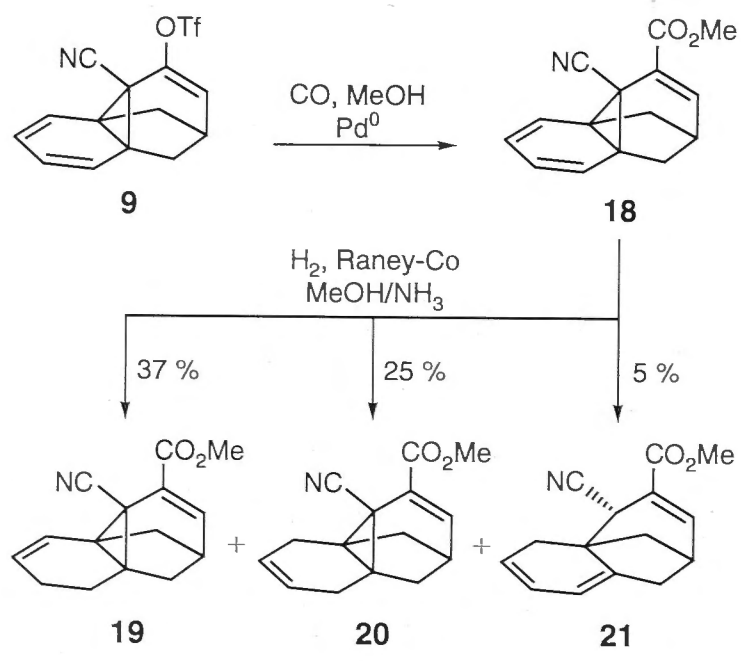


Scheme 2. Compounds produced by reduction of compound **2** under the conditions described in Table 1.

Table 1. Products from reaction of compound 2 with hydrogen in the presence of various catalysts

Entry	Reaction conditions[A]	Product (Yield [%])		
1	H_2, Raney-Co, MeOH/NH_3, 18°C	**12** (5)	**13** (40)	**14** (50)
2	H_2, Rh on Al_2O_3, EtOAc, 18°C	**15** (25)	**16** (50)	**17** (8)
3	H_2, Pd on C, EtOAc, 18°C	**16** (11)	**17** (54)	–

[A]See Experimental section for details.



Scheme 3. Compounds produced by reduction of compound **18** with hydrogen in the presence of Raney-cobalt.

resistance through enhanced drug efflux. Unfortunately, an authentic sample of salvileucalin B was not available to us and nor were the cell lines used by Takeya in testing this natural product.[1] In the event, each of compounds **2** and **12–17** had IC_{50} values of >100 μM in the relevant assays (see the Experimental section and Supplementary Material for details) except in the case of compound **15** which displayed an IC_{50} of 83 μM when tested in the SW620 cell line. Clearly, even though many of these synthetic materials embody an α-alkylidene-γ-butyrolactone residue they are not particularly cytotoxic. The origins of this situation are under investigation.

In a separate set of evaluations to test whether or not compounds **2** and **12–17** posses any capacity to inhibit P-gp-based multidrug resistance mechanisms displayed by numerous human cancer cell lines, they were subjected to a flow cytometry-based calcein AM assay. Once again, however, no significant activity was observed with all the compounds displaying calcein FAR (fluorescence arbitrary ratio) values in the range 0.54 to 0.71 as compared with the value of 43.5 measured for the positive control verapamil at the same concentration.

Conclusions

The intramolecular Büchner reaction has provided a highly effective means for assembling the [4.3.1]propellane substructure **2** associated with the cytotoxic neoclerodane natural product salvileucalin B (**1**). Furthermore, reduction of the former compound under a variety of conditions has provided a suite of partially or fully saturated derivatives, namely compounds **12–17**, which have been used to probe for the pharmacophore of natural product **1**.

The lack of cytotoxic effects displayed by compounds **2** and **12–17** suggest that the second lactone ring and the furan moiety incorporated within the natural product **1** are contributing in a significant way to its biological properties. Accordingly, we are now studying means by which the meso compound **2** can be elaborated, using desymmetrising acylation or alkylation protocols, so as to incorporate one or both of these residues and, thereby, deliver enantiomerically enriched compounds displaying useful cytotoxicities. Results will be reported in due course.

Experimental

General Experimental Protocols

Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at 18°C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^1H NMR data are recorded as follows: chemical shift (δ) (multiplicity, coupling constant(s) J (Hz), relative integral) where multiplicity is defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ 'triplet' appearing at δ_C 77.0 were used to reference the ^1H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analysed as thin films on KBr plates. A VG Fisons AutoSpec mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray ionisation (ESI) mass spectra were obtained on a VG Quattro II triple-quadrupole MS instrument operating in positive ionisation mode. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate/potassium

carbonate/5 % aqueous sodium hydroxide/water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[11] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem, or Lancaster chemical companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH, or Unilab chemical companies. Tetrahydrofuran (THF), methanol, and DCM were dried using a Glass Contour solvent purification system that was based upon a technology originally described by Grubbs et al.[12] Where necessary, reactions were performed under an argon atmosphere.

Specific Experimental Procedures

Compound ***4***

Following the procedure of Ksander,[7] a magnetically stirred a suspension of NaH (1.31 g of a 60 % dispersion in mineral oil, 54.5 mmol) in THF (45 mL) was cooled to 0°C and trimethyl phosphonoacetate (8.8 mL, 9.92 g, 54.5 mmol) then added dropwise. The resulting thick white suspension was stirred at 18°C for 0.5 h and then cooled to 0°C before being treated, dropwise, with a solution of 2-indanone (**3**) (3.00 g, 22.7 mmol, Aldrich) in THF (45 mL). The ensuing brown reaction mixture was stirred at 18°C for 1 h before being poured into brine (100 mL) and extracted with diethyl ether (2 × 40 mL). The combined organic phases were washed with brine (1 × 100 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the brown oil thus obtained to flash chromatography (silica, pentane → 7 : 3 v/v pentane/diethyl ether gradient elution) afforded, after concentration of the appropriate fractions (R_F 0.4 in 85 : 15 v/v hexane/ethyl acetate), the title compound **4**[7] (4.18 g, 98 %) as a white crystalline solid, mp 87–89°C (Found: $M^{+\bullet}$, 188.0835. $C_{12}H_{12}O_2$ requires: $M^{+\bullet}$, 188.0837). δ_H ($CDCl_3$, 300 MHz) 7.41 (d, *J* 8.0, 1H), 7.32 (d, *J* 4.0, 1H), 7.24 (t, *J* 8.0, 1H), 7.15 (m, 1H), 6.70 (s, 1H), 3.72 (s, 3H), 3.54 (s, 2H), 3.45 (s, 2H). δ_C ($CDCl_3$, 75 MHz) 171.4 (C), 144.7 (C), 143.4 (C), 140.9 (C), 130.1 (CH), 126.3 (CH), 124.4 (CH), 123.5 (CH), 120.6 (CH), 52.0 (CH_3), 41.3 (CH_2), 36.8 (CH_2). ν_{max} KBr/cm^{-1} 3056, 3020, 2923, 1740, 1461, 1435, 1169, 753, 717. *m/z* (EI, 70 eV) 188 ($M^{+\bullet}$, 32 %), 149 (12), 129 (100), 128 (75), 84 (35).

Compound ***5***

A magnetically stirred solution of the α,β-unsaturated ester **4** (4.18 g, 22.23 mmol) in ethyl acetate (100 mL) was treated with 10 % palladium on carbon (1.18 g) and the flask containing the resulting mixture was degassed and then filled with hydrogen three times. The reaction mixture was then left stirring under an atmosphere of hydrogen for 5 h before being filtered through Celite. The filtrate was concentrated under reduced pressure to give the title ester **5**[7] (4.22 g, 99 %) as a crystalline solid, mp 32–35°C (Found: $M^{+\bullet}$, 190.0991. $C_{12}H_{14}O_2$ requires: $M^{+\bullet}$, 190.0994). δ_H ($CDCl_3$, 300 MHz) 7.22–7.10 (complex m, 4H), 3.70 (s, 3H), 3.15 (dd, *J* 20.0 and 10.4, 2H), 2.89 (septet, *J* 10.4, 1H), 2.65 (dd, *J* 20.0 and 10.4, 2H), 2.51 (d, *J* 10.4, 2H). δ_C ($CDCl_3$, 75 MHz) 173.4 (C), 142.6 (C), 126.3 (CH), 124.4 (CH), 51.5 (CH_3), 39.7 (CH_2), 38.9 (CH_2), 36.0 (CH). ν_{max} KBr/cm^{-1} 3022, 2926, 1739, 1436, 1199, 1151, 742. *m/z* (EI, 70 eV) 190 ($M^{+\bullet}$, 20 %), 116 (100), 84(60).

This material was used without purification in the next step of the reaction sequence.

Compound ***6***

LiHMDS (2.1 mL of 1 M solution in THF, 2.10 mmol) was added to THF (6 mL) and the resulting solution stirred magnetically while being cooled to −78°C under a nitrogen atmosphere. Dry acetonitrile (82 μL, 1.58 mmol) was then added dropwise to this solution and after 1 h a solution of the ester **5** (200 mg, 1.05 mmol) in THF (4 mL) was added slowly. The ensuing mixture was allowed to warm to 18°C and stirred at this temperature for 16 h before being treated with diethyl ether (10 mL), HCl (5 mL of a 1 M aqueous solution), and brine (10 mL). The separated aqueous phase was extracted with ether (3 × 10 mL) and the combined organic phases washed with brine (2 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the ensuing light-yellow oil to flash chromatography (silica, 1 : 1 v/v pentane/diethyl ether elution) afforded, after concentration of the appropriate fraction (R_F 0.1 in 15 : 85 v/v ethyl acetate/hexane), the *β-keto nitrile* ***6*** (205 mg, 98 %) as a white, crystalline solid, mp 107–108°C (Found: $M^{+\bullet}$, 199.1000. $C_{13}H_{13}NO$ requires: $M^{+\bullet}$, 199.0997). δ_H ($CDCl_3$, 300 MHz) 7.22–7.12 (complex m, 4H), 3.46 (s, 2H), 3.19 (dd, *J* 20.4 and 9.6, 2H), 2.94 (m, 1H), 2.82 (d, *J* 9.6, 2H), 2.59 (dd, *J* 20.4 and 8.8, 2H). δ_C ($CDCl_3$, 75 MHz) 196.8 (C), 142.1 (C), 126.5 (CH), 124.5 (CH), 113.7 (C), 47.8 (CH_2), 38.8 (CH_2), 34.5 (CH_2), 32.2 (CH). ν_{max} KBr/cm^{-1} 3026, 2920, 2258, 1729, 1398, 1109, 1088, 1053. *m/z* (EI, 70 eV) 199 ($M^{+\bullet}$, 2 %), 129 (5), 116 (100), 91 (6).

Compound 7

A magnetically stirred solution of β-keto nitrile **6** (380 mg, 1.91 mmol) in acetonitrile (20 mL) was treated with imidazole sulfonyl azide (396 mg, 2.29 mmol) and pyridine (0.77 mL, 9.54 mmol) and the ensuing pale-yellow reaction mixture was heated at 40°C for 20 h and then concentrated under reduced pressure (CAUTION – diazo compounds are potentially explosive) to give an orange oil. Subjection of this material to flash column chromatography (silica, 3 : 2 v/v pentane/diethyl ether) gave, after concentration of the appropriate fractions (R_F 0.7 in 65 : 35 v/v hexane/ethyl acetate), *compound 7* (415 mg, 1.84 mmol, 96 %) as fine-yellow needles, mp 90°C (with decomposition) (Found: $M^{+\bullet}$, 225.0908. $C_{13}H_{11}N_3O$ requires: $M^{+\bullet}$, 225.0902). δ_H ($CDCl_3$, 300 MHz) 7.22–7.12 (complex m, 4H), 3.17 (dd, *J* 15.6 and 8.0, 2H), 2.97 (septet, *J* 8.0, 1H), 2.82 (d, *J* 8.0, 2H), 2.66 (dd, *J* 15.6 and 8.0, 2H). δ_C ($CDCl_3$, 75 MHz) 189.5 (C), 142.1 (C), 126.5 (CH), 124.5 (CH), 108.4 (C), 44.9 (CH_2), 38.8 (CH_2), 35.5 (CH) (signal due to carbon bearing the diazo group not observed). ν_{max} KBr/cm^{-1} 2934, 2227, 2136, 1673, 1374, 1228, 1187, 1004. *m/z* (EI, 70 eV) 225 ($M^{+\bullet}$, 1 %), 197 (15), 129 (15), 116 (100), 115 (55), 91 (22).

Compound ***8***

A magnetically stirred dispersion of $Rh_2(OAc)_4$ (19 mg, 0.04 mmol, 5 mol %) in DCM (70 mL) was heated at reflux and then treated with a solution of compound **7** (200 mg, 0.89 mmol) in DCM (20 mL) at a rate of 0.2 mmol h^{-1} (using a syringe pump). After addition was complete, the reaction mixture was cooled and then concentrated under reduced pressure to give a white to purple coloured solid. Recrystallisation (THF) of this material gave *compound* ***8*** (430 mg, 86 %) as a white, crystalline solid, mp 194–200°C (Found: $M^{+\bullet}$, 197.0836.

$C_{13}H_{11}NO$ requires: $M^{+\bullet}$, 197.0841). δ_H ($CDCl_3$, 300 MHz) 6.36 (m, 2H), 6.21 (m, 2H), 2.31 (m, 3H), 2.16 (br s, 4H). δ_C ($CDCl_3$, 75 MHz) 199.8 (C), 127.1 (CH), 123.4 (CH), 112.2 (C), 50.4 (CH_2), 43.2 (CH_2), 36.2 (C), 29.3 (C), 25.1 (CH). ν_{max} KBr/cm^{-1} 3050, 2979, 2953, 2873, 2238, 1698, 1447, 1430, 1407, 1395, 1336, 1311, 1292, 1255, 1166, 1143, 1035, 972, 793. *m/z* (EI, 70 eV) 197 ($M^{+\bullet}$, 70 %), 153 (100), 141 (58), 128 (75), 115 (55).

Compound ***9***

A solution of compound **8** (200 mg, 1.01 mmol) in DCM (3 mL) was added to THF (20 mL) and the resulting magnetically stirred mixture cooled to −78°C and then treated, dropwise, with LiHMDS (1.42 mL of a 1 M solution in THF, 1.42 mmol). After a further 0.33 h *N*-phenyl triflimide (471 mg, 1.32 mmol) was added in one portion then the reaction mixture allowed to warm to 18°C and stirred at this temperature for 16 h before being concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 7 : 3 → 1 : 9 v/v pentane/diethyl ether gradient elution) and concentration of the appropriate fractions (R_F 0.5 in 65 : 35 v/v hexane/ethyl acetate) gave *the enol triflate* ***9*** (310 mg, 93 % at 95 % conversion) as white flakes, mp 79°C (with decomposition) (Found: $M^{+\bullet}$, 329.0338. $C_{14}H_{10}F_3NO_3S$ requires: $M^{+\bullet}$, 329.0333). δ_H ($CDCl_3$, 400 MHz) 6.33 (m, 2H), 6.06 (m, 3H), 2.67 (m, 1H), 1.88 (dd, *J* 16.8 and 6.4, 2H), 1.46 (d, *J* 16.8, 2H). δ_C ($CDCl_3$, 100 MHz) 137.2 (C), 127.0 (CH), 120.9 (CH), 118.4 (quartet, J_{C-F} 321), 115.1 (CH), 112.0 (C), 43.0 (C), 31.5 (CH_2), 26.6 (CH), 15.9 (C). δ_F ($CDCl_3$, 400 MHz) −73.0 (s, 3F). ν_{max} KBr/cm^{-1} 2933, 2237, 1656, 1425, 1205, 1140, 964. *m/z* (EI, 70 eV) 329 ($M^{+\bullet}$, 60 %), 196 (56), 168 (100), 153 (55), 141 (93), 115 (48).

Compound ***11***

Step i. Under protection from light, a magnetically stirred solution of nitrile **9** (200 mg, 0.61 mmol) in DCM (5 mL) was cooled to −40°C and then treated, dropwise, with DIBAL-H (1.2 mL of a 1 M solution in hexane, 1.22 mmol). The ensuing mixture was stirred at this temperature for 1 h before being treated with ethyl acetate (0.5 mL) and then allowed to warm to 18°C and quenched with HCl (1 mL of a 1 M aqueous solution), a process that resulted in the development of a bright-yellow colouration in the organic phase which thickened over time. The reaction mixture was stirred vigorously for ~0.33 h and then the separated organic phase was concentrated under a stream of nitrogen. The resulting yellow oil was subjected to flash chromatography (silica, 4 : 1 v/v pentane/diethyl ether elution) and concentration of the appropriate fractions (R_F 0.9 in 65 : 35 v/v hexane/ethyl acetate) gave a bright-yellow oil that was immediately resubjected to treatment with DIBAl-H as specified immediately below.

Step ii. A magnetically stirred solution of the bright-yellow oil obtained in *step i* in DCM (5 mL) was cooled to −78°C and then treated dropwise with DIBAl-H (1.8 mL of a 1 M solution in DCM) and the resulting mixture allowed to warm to 18°C over 16 h before being treated with ethyl acetate (0.5 mL) and then HCl (1 mL of a 1 M aqueous solution). The resulting viscous mixture was diluted with DCM (5 mL) and then stirred vigorously for 0.5 h. The separated aqueous phase was extracted with DCM (2 × 4 mL) and the combined organic phases were then washed with water (1 × 5 mL) before bring dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 3 : 2 v/v pentane/diethyl ether elution) gave, after concentration of the appropriate fractions (R_F 0.6 in 65 : 35 v/v hexane/ethyl acetate), *the title alcohol* ***11*** (33 mg, 16 %) as a white, crystalline solid, mp 54–58°C (Found: $M^{+\bullet}$, 334.0489. $C_{14}H_{13}F_3O_4S$ requires: $M^{+\bullet}$, 334.0487). δ_H ($CDCl_3$, 300 MHz) 6.09 (m, 2H), 6.02 (m, 3H), 3.63 (d, *J* 5.3, 2H), 2.45 (m, 1H), 1.66 (dd, *J* 16.4 and 4.8, 2H), 1.47 (d, *J* 16.4, 2H) (signal due to OH group proton not observed). δ_C ($CDCl_3$, 75 MHz) 143.9 (C), 125.2 (CH), 122.9 (CH), 118.4 (q, $J_{C,F}$ 320, CF_3), 115.7 (CH), 55.8 (CH_2), 37.5 (C), 33.2 (CH_2), 26.5 (CH), 23.1 (C). ν_{max} KBr/cm^{-1} 3436, 3036, 2929, 2859, 1653, 1418, 1247, 1208, 1139, 1009, 971, 892, 809. *m/z* (EI, 70 eV) 334 ($M^{+\bullet}$, 95 %), 201 (20), 183 (45), 155 (85), 129 (100), 128 (77), 116 (74), 115 (85).

Compound ***2***

A magnetically stirred solution of alcohol **11** (44 mg, 0.13 mmol) in THF (2.5 mL) was treated with $Pd(PPh_3)_4$ (15 mg, 0.0132 mmol, 10 mol %), LiCl (11 mg, 0.264 mmol), and triethylamine (73 μL, 0.526 mmol). The reaction flask was evacuated and then refilled with carbon monoxide three times before being stirred under an atmosphere of carbon monoxide at 18°C for 4 h. After this time the reaction mixture was sparged with nitrogen and then concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 7 : 3 v/v pentane/diethyl ether) gave, after concentration of the appropriate fractions (R_F 0.6 in 65 : 35 v/v hexane/ethyl acetate), the *title lactone* ***2*** (25 mg, 89 %) as colourless, crystals, mp 105–110°C (Found: $M^{+\bullet}$, 212.0840. $C_{14}H_{12}O_2$ requires: $M^{+\bullet}$, 212.0837). δ_H ($CDCl_3$, 400 MHz) 7.07 (d, *J* 6.8, 1H), 6.14 (m, 2H), 5.92 (m, 2H), 3.89 (s, 2H), 2.90 (m, 1H), 1.74 (dd, *J* 11.6 and 4.4, 2H), 1.25 (d, *J* 11.6, 2H). δ_C ($CDCl_3$, 100 MHz) 169.5 (C), 132.3 (CH), 125.2 (C), 123.6 (CH), 122.1 (CH), 67.1 (CH_2), 37.8 (CH), 30.8 (C), 30.2 (CH_2), 22.7 (C). ν_{max} KBr/cm^{-1} 2949, 2927, 1755, 1652, 1234, 1072, 1040, 1005, 750. *m/z* (EI, 70 eV) 212 ($M^{+\bullet}$, 90 %), 197 (50), 183 (65), 167 (92), 155 (100), 153 (75), 152 (65), 115 (62).

Compounds ***12–14***

A magnetically stirred solution of lactone **2** (12 mg, 0.06 mmol) in ammoniacal methanol (2 mL) maintained under a nitrogen atmosphere at 18°C was treated with Raney-cobalt (spatula tip full of catalyst maintained as a slurry in MeOH/H_2O). The flask containing the ensuing mixture was then flushed three times with hydrogen before a balloon of hydrogen was attached to it. After 0.5 h the reaction mixture was flushed with nitrogen and then filtered through Celite and the filtrate concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash chromatography (silica, 4 : 1 v/v pentane/diethyl ether elution) gave three fractions, A, B, and C.

Concentration of fraction A (R_F 0.6 in 65 : 35 v/v hexane/ethyl acetate) gave *compound* ***12*** (0.6 mg, 5 %) as a white, crystalline solid (Found: $M^{+\bullet}$, 214.0993. $C_{14}H_{14}O_2$ requires: $M^{+\bullet}$, 214.0994). δ_H ($CDCl_3$, 400 MHz) 6.99 (d, *J* 9.6, 1H), 5.97 (m, 1H), 5.82 (m, 1H), 4.41 (d, *J* 12.8, 1H), 4.13 (d, *J* 12.8, 1H), 2.94 (m, 1H), 2.27 (m, 1H), 1.99 (m, 1H), 1.90–1.40 (complex m, 4H), 1.00 (m, 2H). δ_C ($CDCl_3$, 100 MHz) 169.6 (C), 134.7 (CH), 126.7 (CH), 126.5 (C), 124.2 (CH), 67.6 (CH_2), 38.4 (C), 33.7 (CH), 33.4 (CH_2), 30.2 (CH_2), 28.8 (C), 28.0 (C), 22.9 (CH_2), 18.9 (CH_2). ν_{max} KBr/cm^{-1} 2926, 2854, 1758, 1653, 1436, 1359, 1239, 1052, 1020, 1009. *m/z* (EI, 70 eV) 214 ($M^{+\bullet}$,

100 %), 199 (10), 186 (32), 169 (22), 155 (26), 141 (28), 129 (29), 128 (30), 115 (31), 91 (31).

Concentration of fraction B (R_F 0.6 in 65 : 35 v/v hexane/ethyl acetate) gave *compound* ***13*** (5 mg, 40 %) as a white, crystalline solid, mp 138–140°C (Found: $M^{+\bullet}$, 214.0992. $C_{14}H_{14}O_2$ requires: $M^{+\bullet}$, 214.0994). δ_H ($CDCl_3$, 400 MHz) 6.93 (d, *J* 6.8, 1H), 5.66 (m, 2H), 4.09 (s, 2H), 2.87 (m, 1H), 2.56 (d, *J* 16.8, 2H), 2.30 (dm, *J* 16.8, 2H), 1.66 (dd, *J* 11.6 and 4.8, 2H), 0.96 (d, *J* 11.6, 2H). δ_C ($CDCl_3$, 100 MHz) 169.7 (C), 133.7 (CH), 126.3 (C), 124.6 (CH), 67.1 (CH_2), 32.9 (CH_2), 32.7 (CH), 31.6 (C), 25.3 (C), 23.6 (CH_2). ν_{max} KBr/cm^{-1} 2923, 1756, 1652, 1431, 1239, 1146, 1084, 1052, 1004. *m/z* (EI, 70 eV) 214 ($M^{+\bullet}$, 100 %), 199 (22), 186 (39), 185 (40), 155 (29), 141 (38), 129 (59), 116 (52), 115 (57), 91 (67), 84 (60), 79 (52).

Concentration of fraction C (R_F 0.7 in 65 : 35 v/v hexane/ethyl acetate) gave *compound* ***14*** (6 mg, 50 %) as a white, crystalline solid, mp 95–99°C (Found: $M^{+\bullet}$, 216.1149. $C_{14}H_{16}O_2$ requires: $M^{+\bullet}$, 216.1150). δ_H ($CDCl_3$, 400 MHz) 5.57 (d, *J* 2.4, 2H), 4.02 (dd, *J* 10.4 and 0.8, 1H), 3.98 (d, *J* 10.4, 1H), 2.89 (dd, *J* 11.6 and 7.9, 1H), 2.45–2.05 (complex m, 4H), 1.90–1.51 (complex m, 7H). δ_C ($CDCl_3$, 100 MHz) 178.6 (C), 124.6 (CH), 124.5 (CH), 67.7 (CH_2), 39.3 (CH_2), 36.8 (CH_2), 35.9 (CH), 29.8 (C), 29.7 (CH), 27.9 (CH_2), 26.6 (CH_2), 26.3 (C), 25.8 (C), 25.5 (CH_2). ν_{max} KBr/cm^{-1} 2851, 1778, 1436, 1365, 1189, 1152, 1078, 1032, 986. *m/z* (EI, 70 eV) 216 ($M^{+\bullet}$, 100 %), 158 (22), 143 (28), 129 (42), 117 (42), 91 (75).

Compounds ***15–17***

A magnetically stirred solution of lactone **2** (12 mg, 0.06 mmol) in ethyl acetate (2 mL) maintained at 18°C was treated with 5 % rhodium on alumina (3 mg). The reaction vessel containing the resulting mixture was flushed three times with hydrogen and then maintained under a balloon of this gas for 0.33 h before being flushed with nitrogen and then filtered through Celite. The filtrate was concentrated under reduced pressure to give a clear, colourless oil that was subjected to flash column chromatography (silica, 4 : 1 v/v pentane/diethyl ether) thus giving three fractions, A, B, and C.

Concentration of fraction A (R_F 0.6 in 65 : 35 v/v hexane/ethyl acetate) gave *compound* ***15*** (3 mg, 25 %) as a white, crystalline solid, mp 85–90°C (Found: $[M+H]^+$, 217.1231. $C_{14}H_{17}O_2$ requires: $[M+H]^+$, 217.1229). δ_H ($CDCl_3$, 400 MHz) 6.92 (d, *J* 7.2, 1H), 4.37 (s, 2H), 2.78 (m, 1H), 1.93 (m, 2H), 1.75–0.80 (complex m, 10 H). δ_C ($CDCl_3$, 100 MHz) 169.8 (C), 133.7 (CH), 126.3 (C), 66.7 (CH_2), 34.2 (CH_2), 33.1 (CH), 31.6 (C), 24.5 (C), 22.0 (CH_2), 21.9 (CH_2). ν_{max} KBr/cm^{-1} 2929, 2853, 1761, 1657, 1450, 1364, 1235, 1072, 1056, 1038, 1010. *m/z* (ESI, +ve) 239 ($[M+Na]^+$, 97 %), 217 ($[M+H]^+$, 100).

Concentration of fraction B (R_F 0.7 in 65 : 35 v/v hexane/ethyl acetate) gave *compound* ***16*** (6 mg, 50 %) as a white, crystalline solid, mp 44–46°C (Found: $M^{+\bullet}$, 218.1312. $C_{14}H_{18}O_2$ requires: $M^{+\bullet}$, 218.1307). δ_H ($CDCl_3$, 400 MHz) 4.29 (d, *J* 9.2, 1H), 4.17 (dd, *J* 9.2 and 1.2, 1H), 2.86 (dd, *J* 11.6 and 8.0, 1H), 2.04 (m, 1H), 1.80–1.05 (complex m, 13H), 0.78 (m, 1H). δ_C ($CDCl_3$, 100 MHz) 178.6 (C), 67.7 (CH_2), 40.5 (CH_2), 37.8 (CH_2), 36.4 (CH), 30.8 (C), 30.1 (CH), 27.6 (CH_2), 26.4 (C), 25.8 (C), 25.0 (CH_2), 24.2 (CH_2), 22.2 (CH_2), 21.5 (CH_2). ν_{max} KBr/cm^{-1} 2930, 2850, 1775, 1447, 1361, 1175, 1145, 1075, 1027, 988. *m/z* (EI, 70 eV) 218 ($M^{+\bullet}$, 100 %), 145 (20), 131 (25), 91 (45).

Concentration of fraction C (R_F 0.5(7) in 65 : 35 v/v hexane/ethyl acetate) gave *compound* ***17*** (1 mg, 8 %) as a white, crystalline solid, mp 85–89°C (Found: $M^{+\bullet}$, 218.1307. $C_{14}H_{18}O_2$ requires: $M^{+\bullet}$, 218.1307). δ_H ($CDCl_3$, 400 MHz) 4.75 (m, 2H), 2.58 (m, 1H), 2.40 (m, 1H), 2.24 (dd, *J* 11.6 and 6.0, 1H), 2.08 (m, 1H), 2.00–1.80 (complex m, 2H), 1.75–1.05 (complex m, 10H). δ_C ($CDCl_3$, 100 MHz) 174.8 (C), 172.3 (C), 123.2 (C), 69.1 (CH_2), 46.4 (CH), 44.1 (C), 38.7 (CH_2), 35.3 (CH_2), 32.5 (CH_2), 32.0 (CH), 31.7 (CH_2), 28.5 (CH_2), 25.5 (CH_2), 20.9 (CH_2). ν_{max} KBr/cm^{-1} 2924, 2850, 1769, 1667, 1432, 1383, 1342, 1299, 1195, 1046, 1018, 1007. *m/z* (EI, 70 eV) 218 ($M^{+\bullet}$, 70 %), 189 (15), 121 (100), 91 (30).

Compounds ***16*** *and* ***17***

Using the same protocol as defined immediately above, a solution of lactone **2** (12 mg, 0.0565 mmol) in ethyl acetate (2 mL) containing 10 % palladium on carbon (2 mg) was subjected to hydrogenation at 18°C for 0.33 h. The crude reaction mixture was then subjected to flash chromatography (silica, 45 : 1 v/v pentane/diethyl ether elution) and thus afforded two fractions, A and B.

Concentration of fraction A (R_F 0.7 in 65 : 35 v/v hexane/ethyl acetate) gave *compound* ***16*** (2 mg, 11 %) as a white, crystalline solid that was identical, in all respects, with the material obtained by the method defined immediately above.

Concentration of fraction B (R_F 0.5(7) in 65 : 35 v/v hexane/ethyl acetate) gave *compound* ***17*** (7 mg, 54 %) as a white, crystalline solid that was identical, in all respects, with the material obtained by the method defined immediately above.

Compound ***18***

A magnetically stirred solution of triflate **9** (80 mg, 0.243 mmol) in THF (3.0 mL) was treated with $Pd(PPh_3)_4$ (28 mg, 0.024 mmol, 10 mol %), triethylamine (135 µL, 0.97 mmol), and methanol (0.79 mL, 19.4 mmol). The reaction flask was evacuated and then refilled with carbon monoxide three times. The reaction mixture was then left stirring under an atmosphere of carbon monoxide at 18°C for 3 h before being sparged with nitrogen and then concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 1 : 1 v/v pentane/diethyl ether) gave, after concentration of the appropriate fractions (R_F 0.3 in 65 : 35 v/v hexane/ethyl acetate), the *title ester* ***18*** (54 mg, 93 %) as colourless crystals, mp 127–130°C (Found: $M^{+\bullet}$, 239.0946. $C_{15}H_{13}NO_2$ requires: $M^{+\bullet}$, 239.0946). δ_H ($CDCl_3$, 400 MHz) 7.10 (d, *J* 8.0, 1H), 6.30 (dd, *J* 7.6 and 2.8, 2H), 5.98 (dd, *J* 7.6 and 2.4, 2H), 3.80 (s, 3H), 2.63 (m, 1H), 1.86 (dd, *J* 12.4 and 5.2, 2H), 1.41 (d, *J* 12.4, 2H). δ_C ($CDCl_3$, 100 MHz) 164.9 (C), 137.5 (CH), 126.8 (CH), 122.2 (C), 121.2 (CH), 114.4 (C), 52.1 (CH_3), 41.9 (C), 30.9 (CH_2), 28.0 (CH), 12.9 (C). ν_{max} KBr/cm^{-1} 3041, 2996, 2927, 2950, 2849, 2232, 1724, 1619, 1438, 1367, 1267, 1191, 1159, 1131, 1096, 1040, 970. *m/z* (EI, 70 eV) 239 ($M^{+\bullet}$, 30 %), 205 (30), 180 (100), 153 (40), 152 (27), 115 (20).

Compounds ***19–21***

A magnetically stirred solution of compound **18** (40 mg, 0.17 mmol) in ammoniacal methanol (2.0 mL) maintained at 18°C was treated with Raney-cobalt (spatula tip full of catalyst maintained as a slurry in aqueous methanol). The reaction vessel containing the resulting mixture was flushed three times with hydrogen and then maintained under a balloon of this gas for 4 h. The reaction mixture was then flushed with nitrogen before being filtered through Celite and the filtrate was concentrated under reduced pressure to give a clear, colourless oil. Subjection

of this material to flash column chromatography (silica, 3 : 7 v/v pentane/diethyl ether) gave three fractions, A, B and C.

Concentration of fraction A (R_F 0.5) gave *compound* ***19*** (15 mg, 37 %) as a white, crystalline solid, mp 130–134°C (Found: $M^{+\bullet}$, 241.1103. $C_{15}H_{15}NO_2$ requires: $M^{+\bullet}$, 241.1103). δ_H ($CDCl_3$, 400 MHz) 7.06 (d, *J* 8.0, 1H), 6.09 (m, 1H), 5.95 (m, 1H), 3.78 (s, 3H), 2.76 (m, 1H), 2.40–2.02 (complex m, 4H), 1.74 (m, 2H), 1.21 (m, 2H). δ_C ($CDCl_3$, 100 MHz) 165.0 (C), 140.2 (CH), 139.8 (C), 132.4 (CH), 121.6 (CH), 117.6 (C), 52.0 (CH_3), 33.8 (CH_2), 33.7 (C), 33.6 (C), 31.6 (CH), 30.8 (CH_2), 29.5 (C), 22.4 (CH_2), 20.2 (CH_2). ν_{max} KBr/cm^{-1} 3031, 2927, 2850, 2230, 1716, 1616, 1433, 1367, 1263, 1189, 1156, 1127, 1098, 850, 760. *m/z* (EI, 70 eV) 241 ($M^{+\bullet}$, 65 %), 226 (100), 209 (35), 182 (70).

Concentration of fraction B (R_F 0.4) gave *compound* ***20*** (10 mg, 25 %) as a white, crystalline solid, mp 150–154°C (Found: $M^{+\bullet}$, 241.1101. $C_{15}H_{15}NO_2$ requires: $M^{+\bullet}$, 241.1103). δ_H ($CDCl_3$, 400 MHz) 7.06 (d, *J* 7.6, 1H), 5.75 (s, 2H), 3.79 (s, 3H), 2.70 (m, 1H), 2.59 (s, 4H), 1.72 (dd, *J* 12.4 and 5.2, 2H), 1.25 (d, *J* 12.4, 2H). δ_C ($CDCl_3$, 100 MHz) 165.1 (C), 139.8 (CH), 124.0 (C), 123.6 (CH), 116.5 (C), 52.0 (CH_3), 34.1 (CH_2), 31.6 (C), 31.2 (CH), 23.8 (CH_2), 23.6 (C). ν_{max} KBr/cm^{-1} 3035, 2995, 2923, 2834, 2229, 1724, 1618, 1440, 1269, 1269, 1210, 1189, 1161, 1122, 1096, 766. *m/z* (EI, 70 eV) 241 ($M^{+\bullet}$, 100 %), 226 (50), 209 (55), 208 (60), 180 (55), 115 (35), 67 (50).

Concentration of fraction C (R_F 0.6) gave *compound* ***21*** (2 mg, 5 %) as a pale-yellow, crystalline solid, mp 133–134°C (Found: $M^{+\bullet}$, 241.1102. $C_{15}H_{15}NO_2$ requires: $M^{+\bullet}$, 241.1103). δ_H ($CDCl_3$, 400 MHz) 7.35 (d, *J* 6.8, 1H), 6.06 (m, 1H), 5.89 (br s, 1H), 5.78 (m, 1H), 3.76 (s, 3H), 3.69 (s, 1H), 2.95–2.83 (m, 2H), 2.60 (dd, *J* 17.0 and 6.5, 1H), 2.46 (d, *J* 17.0, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 1.60 (dd, *J* 11.9 and 3.8, 1H). δ_C ($CDCl_3$, 100 MHz) 165.4 (C), 147.8 (CH), 143.0 (C), 126.0 (CH), 124.1 (C), 122.4 (CH), 120.1 (CH), 118.6 (C), 52.1 (CH_3), 41.6 (C), 39.1 (2 × CH_2), 35.0 (CH), 34.1 (CH), 32.7 (CH_2). ν_{max} KBr/cm^{-1} 3041, 2951, 2867, 2233, 1718, 1644, 1435, 1361, 1285, 1247, 1112, 977. *m/z* (EI, 70 eV) 241 ($M^{+\bullet}$, 40 %), 182 (50), 125 (48), 116 (62), 117 (80), 91 (100).

Crystallographic Studies

Data for Compound **2**

$C_{14}H_{12}O_2$, *M* 212.25, *T* 200 K, triclinic, space group $P\bar{1}$, *Z* 2, *a* 8.0384(2), *b* 8.2320(2), *c* 8.7349(2) Å; α 79.3581(14)°, β 80.7333(17)°, γ 65.1725(14)°; *V* 513.30(2) $Å^3$, D_x 1.373 g cm^{-3}, 2995 unique data ($2\theta_{max}$ 60°), *R* 0.040 [for 2512 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.101 (all data), *S* 0.98.

Data for Compound **8**

$C_{13}H_{11}NO$, *M* 197.24, *T* 200 K, triclinic, space group $P\bar{1}$, *Z* 2, *a* 6.7916(3), *b* 8.2851(3), *c* 9.0747(3) Å; α 75.690(3)°, β 83.678(2)°, γ 88.747(2)°; *V* 491.76(3) $Å^3$, D_x 1.332 g cm^{-3}, 2236 unique data ($2\theta_{max}$ 55°), *R* 0.040 [for 1812 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.098 (all data), *S* 0.98.

Data for Compound **17**

$C_{14}H_{18}O_2$, *M* 218.30, *T* 200 K, monoclinic, space group $P2_1/c$, *Z* 4, *a* 6.6120(2), *b* 11.4845(5), *c* 14.9989(6) Å; β 90.017(2)°; *V* 1138.95(8) $Å^3$, D_x 1.273 g cm^{-3}, 2558 unique data ($2\theta_{max}$ 55°), *R* 0.039 [for 2206 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.102 (all data), *S* 1.00.

Data for Compound **21**

$C_{15}H_{15}O_2$, *M* 241.29, *T* 200 K, monoclinic, space group *C*2/c, *Z* 8, *a* 20.7142(5), *b* 7.7593(1), *c* 15.8461(4) Å; β 105.3732(12)°; *V* 2455.78(9) $Å^3$, D_x 1.305 g cm^{-3}, 2816 unique data ($2\theta_{max}$ 55°), *R* 0.050 [for 2348 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.139 (all data), *S* 1.02.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, λ 0.71073 Å) and data extracted using the DENZO package.[13] Structure solution was by direct methods (SIR92).[14] The structures of compounds **2**, **8**, **17**, and **21** were refined using the CRYSTALS program package.[15] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 883755–883758 for compounds **2**, **8**, **17**, and **21**, respectively). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif.

Biological Studies

Cytotoxicity Assays

A 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to evaluate the cytotoxicity of compounds **2** and **12–17** against the relevant cancer cell line. This assay was modified slightly from that previously described.[16] Briefly, cells (2000 per well in 180 μL of RPMI 1640 supplemented with 10 % fetal bovine serum (FBS) for SW620 and SW620 Ad300, 3000 or 5000 per well in 180 μL of Dulbecco's modied Eagle's medium (DMEM) supplemented with 10 % FBS for KB-3-1 and KB-V1, respectively) were seeded evenly in a 96-well micro-plate, and the plate was incubated for 18 h (37°C; 5 % CO_2) to allow cells to attach. The compounds to be tested were dissolved in 5 % DMSO (v/v) and diluted from 1 mM to 300 nM. Aliquots (20 μL) of each dilution (or of 5 % aqueous DMSO for control wells) were added to the plate in duplicate. After 68 h of incubation (37°C; 5 % CO_2), a solution of MTT (Sigma, USA) in phosphate-buffered saline (PBS) was added to each well to a final concentration of 0.4 mg mL^{-1} and the plate was incubated for a further 4 h (37°C; 5 % CO_2). After that time, the medium was carefully aspirated and precipitated formazan crystals were dissolved in DMSO (100 μL per well). Finally, the absorbance of each well was measured at 570 nm using a PowerWave XS Microplate Reader from Bio-Tek Instruments Inc. (Vinooski, VT). The IC_{50} value was calculated as the concentration of the compound required for 50 % inhibition of the cancer cells using *Prism 5.0* from GraphPad Software Inc. (La Jolla, CA). Results are presented in the Supplementary Material.

Flow Cytometry (Calcein AM Assay)

The flow cytometry assay was a modification of that described previously.[17] Thus, cells which overexpress P-gp (SW620 Ad300) were harvested with trypsin and resuspended in completed medium to give a final concentration of 50 × 10^4 cells mL^{-1} and pre-incubated with 20 μM solutions of the synthetic analogues or verapamil for 0.5 h at 37°C in 5 % CO_2. Cells were then incubated with 2.5 μM calcein AM for 1 h before being washed twice with cold PBS. Samples were analysed on a BD FACSCanto™ II flow cytometer (Becton Dickinson, San Jose, CA). Calcein fluorescence was detected with a 488 nm

argon laser and a 530 nm band-pass filter. Data were analysed by *FCSexpress 3* (*De Novo* Software, Los Angeles, CA). For each sample, 10 000 events were collected. Inhibition was evaluated using the following equation: FAR (fluorescence arbitrary ratio) = calcein fluorescence intensity (Geo mean) in the presence of the synthetic analogues at 20 μM/calcein fluorescence intensity (Geo mean) in the presence of PBS. The positive control was a 20 μM solution of verapamil which displayed a FAR of 43.5.

Supplementary Material

The X-ray crystal structures for compounds **8**, **17**, and **21**, cytotoxicity results for compounds **2** and **12–17**, and ^{1}H or ^{13}C NMR spectra of compounds **2**, **4–9**, and **11–21** are available on the Journal's website.

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References

[1] Y. Aoyagi, A. Yamazaki, C. Nakatsugawa, H. Fukaya, K. Takeya, S. Kawauchi, H. Izumi, *Org. Lett.* **2008**, *10*, 4429. doi:10.1021/OL801620U

[2] C.-C. Tseng, H. Ding, A. Li, Y. Guan, D. Y.-K. Chen, *Org. Lett.* **2011**, *13*, 4410. doi:10.1021/OL201748X

[3] R. R. A. Kitson, A. Millemaggi, R. J. K. Taylor, *Angew. Chem. Int. Ed.* **2009**, *48*, 9426. doi:10.1002/ANIE.200903108

[4] J. H. Van Drie, *Internet Electron. J. Mol. Des.* **2007**, *6*, 271.

[5] For a useful review covering this reaction see: H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977. doi:10.1021/CR010007E

[6] (a) S. Levin, R. R. Nani, S. E. Reisman, *J. Am. Chem. Soc.* **2011**, *133*, 774. doi:10.1021/JA110192B
(b) Also see: S. Levin, R. R. Nani, S. E. Reisman, *Org. Lett.* **2010**, *12*, 780. doi:10.1021/OL902848K

[7] G. M. Ksander, R. deJesus, A. Yuan, C. Fink, M. Moskal, E. Carlson, P. Kukkola, N. Bilci, E. Wallace, A. Neubert, D. Feldman, T. Mogelesky, K. Poirier, M. Jeune, R. Steele, J. Wasvery, Z. Stephan, E. Cahill, R. Webb, A. Navarrete, W. Lee, J. Gibson, N. Alexander, H. Sharif, A. Hospattankar, *J. Med. Chem.* **2001**, *44*, 4677. doi:10.1021/JM010294E

[8] Z. Puterová, A. Andicsová, D. Végh, *Tetrahedron* **2008**, *64*, 11262. doi:10.1016/J.TET.2008.09.032

[9] (a) E. D. Goddard-Borger, R. V. Stick, *Org. Lett.* **2007**, *9*, 3797. doi:10.1021/OL701581G
(b) Also see: N. Fischer, E. D. Goddard-Borger, R. Greiner, T. M. Klapötke, B. W. Skelton, J. Stierstorfer, *J. Org. Chem.* **2012**, *77*, 1760. doi:10.1021/JO202264R

[10] (a) For related examples of cyclopropane ring cleavage reactions see: M. T. Wuesthoff, B. Rickborn, *J. Org. Chem.* **1968**, *33*, 1311. doi:10.1021/JO01267A111
(b) F. Zutterman, A. Krief, *J. Org. Chem.* **1983**, *48*, 1135. doi:10.1021/JO00155A052

[11] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923. doi:10.1021/JO00408A041

[12] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518. doi:10.1021/OM9503712

[13] Z. Otwinowski, W. Minor, Processing of X-Ray Diffraction Data Collected in Oscillation Mode, in *Methods in Enzymology, Volume 276: Macromolecular Crystallography, Part A* (Eds C. W. Carter, Jr, R. M. Sweet) 1997, pp. 307–326 (Academic Press: New York, NY).

[14] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Cryst.* **1994**, *27*, 435.

[15] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Cryst.* **2003**, *36*, 1487. doi:10.1107/S0021889803021800

[16] C. J. Henrich, H. R. Bokesch, M. Dean, S. E. Bates, R. W. Robey, E. I. Goncharova, J. A. Wilson, J. B. McMahon, *J. Biomol. Screen.* **2006**, *11*, 176. doi:10.1177/1087057105284576

[17] C. J. Henrich, R. W. Robey, K. Takada, H. R. Bokesch, S. E. Bates, S. Shukla, S. V. Ambudkar, J. B. McMahon, K. R. Gustafson, *ACS Chem. Biol.* **2009**, *4*, 637. doi:10.1021/CB900134C

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Reversible Cyclopropane Ring-Cleavage Reactions within Etheno-Bridged [4.3.1]Propelladiene Frameworks Leading to Aza- and Oxa-[5.6.5.6]fenestratetraenes

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In 2008 Takeya and co-workers reported[1] on the isolation and structural elucidation of the [5.3.1]propellane-containing and biologically active neoclerodane salvileucalin B (**1**, Figure 1). In connection with efforts to probe the origins of the cytotoxic effects of this natural product, we recently developed a synthesis of the key substructure **2**.[2] Part of the associated reaction sequence involved reduction of nitrile **3** to primary alcohol **4**. This proved to be an unexpectedly complex process because of the intervention of remarkable and reversible cyclopropane ring-cleavage processes leading to the formation (and disassembly) of aza- and oxa-[5.6.5.6]fenestratetraenes. These compounds represent unusual new examples of fenestranes that, as a class, continue to attract considerable attention because of the capacity they provide to examine the "plasticity" of the tetrahedral geometry normally imposed on sp^3-hybridized carbon atoms by virtue of the bonding in such systems.[3] Details are presented herein.

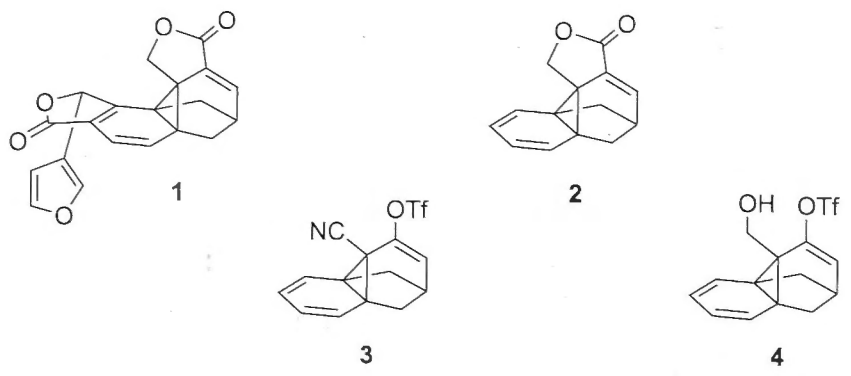

Figure 1. The natural product salvileucalin B (**1**) and related substructures. Tf = trifluoromethanesulfonyl.

Our initial attempts to effect the conversion of **3** into **4** involved treating the first compound with DIBAl-H in dichloromethane (CH_2Cl_2) at −40 °C and then quenching the reaction mixture with Rochelle's salt. It was anticipated that this would provide the corresponding aldehyde. However, the only products of this reaction were the aza-[5.6.5.6]fenestratetrene **5** (15 %) and its oxa analogue **6** (variable yields), both of which proved to be rather unstable compounds (Figure 2). When the reaction mixture was quenched with aqueous HCl (rather than Rochelle's salt) then compound **6** (49 %) was the exclusive product of reaction. The structure of compound **5** was established by single-crystal X-ray analysis whereas that of congener **6** followed from the equivalent analysis of the readily obtained 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[4] adduct **7** (53 %), itself a bridged fenestrane.[5]

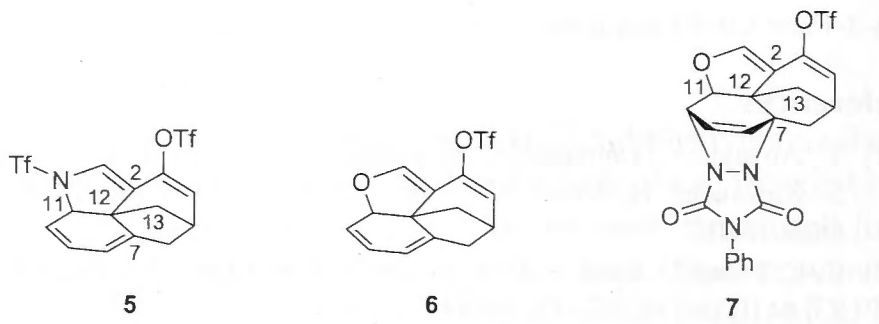

Figure 2. Fenestranes **5**, **6**, and **7**.

The bond angles, as determined by the above-mentioned X-ray analyses, about the central carbon atoms (C12 in each case) of compounds **5** and **7** are shown in Table 1. These data reveal that in each case there is some significant[3] deviation from tetrahedral geometry imposed on the central carbon atom by the surrounding framework, both in terms of angle compression (down to 100°) and angle widening

Table 1. Bond angles, as determined by X-ray analysis, about the central carbon atoms (C12) of fenestranes **5** and **7**.

Compound **5**		Compound **7**	
Atom array	Bond angle [°]	Atom array	Bond angle [°]
C2-C12-C7	112.7(2)	C2-C12-C7	113.5(2)
C2-C12-C11	102.60(19)	C2-C12-C11	101.5(2)
C2-C12-C13	104.61(19)	C2-C12-C13	107.2(2)
C7-C12-C11	115.1(2)	C7-C12-C11	109.4(2)
C7-C12-C13	100.5(2)	C7-C12-C13	100.1(2)
C11-C12-C13	121.2(2)	C11-C12-C13	126.0(2)

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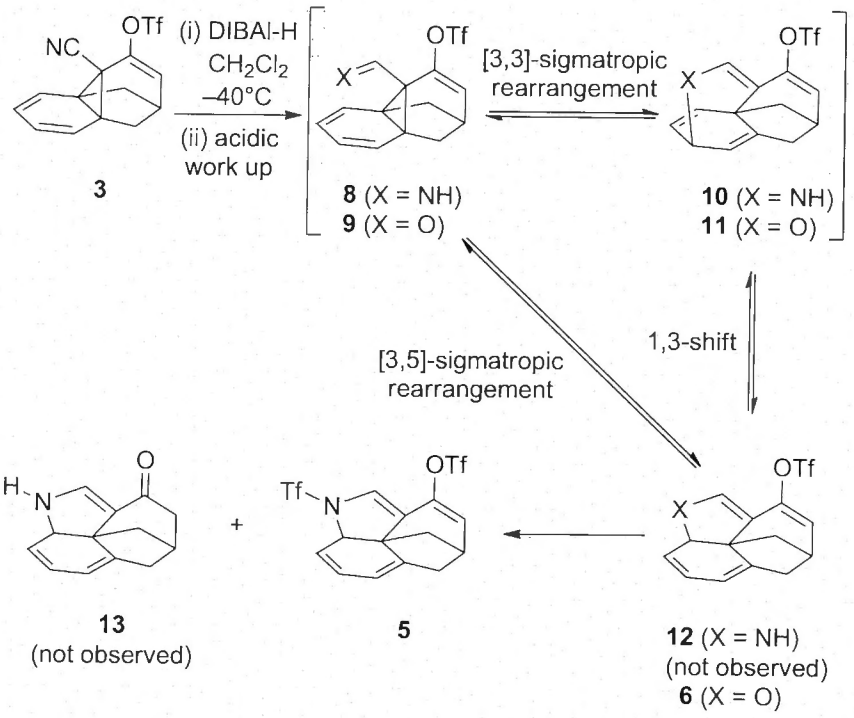
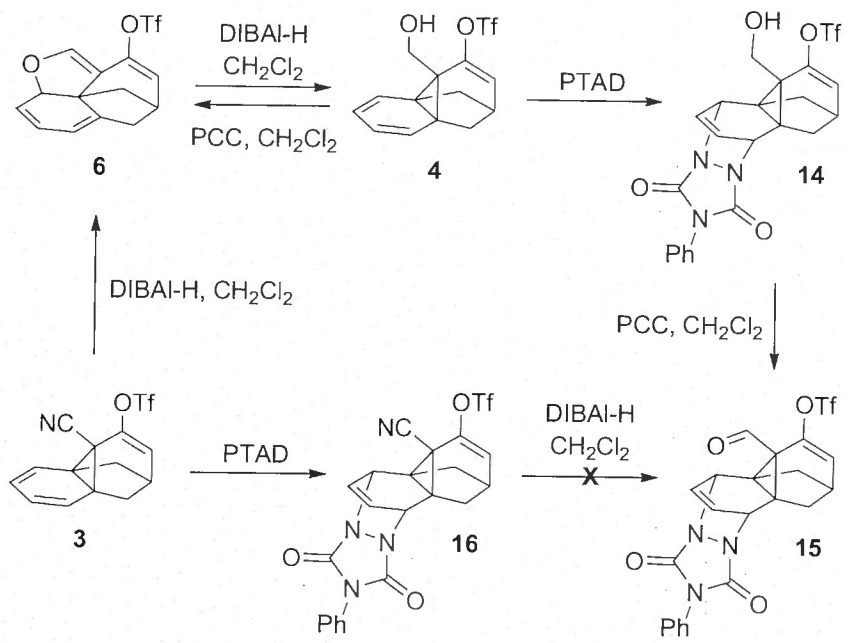


Scheme 1. Possible pathways to fenestratetraenes **5** and **6** from nitrile **3**.



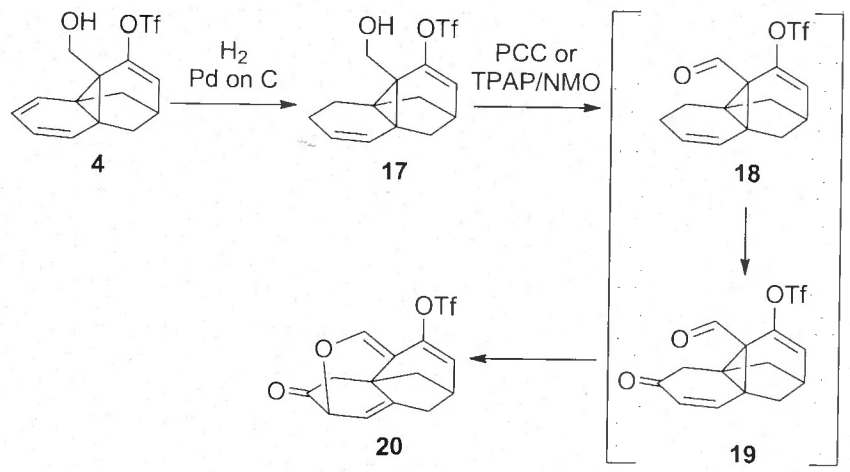
Scheme 2. The interconversion of compounds **4** and **6**.

(up to 126°) and thus further emphasizing the "plasticity" in the spatial arrangements of groups attached to an sp^3-hybridized carbon atom.

Two possible pathways to fenestratetraenes **5** and **6** are outlined in Scheme 1. Thus, either the initially formed imine **8** or the corresponding aldehyde **9** could engage in a [3,3]-sigmatropic rearrangement to deliver the cyclopropane-ring-cleavage products **10** and **11**, respectively. These could, in turn, participate in either a nonconcerted 1,3-nitrogen or a nonconcerted 1,3-oxygen shift (allylic rearrangement) to give compounds **12** and **6**, respectively. Compound **12** was not isolated because of the intervention of a Tf-group transfer reaction leading to the observed product (**5**) and (presumably) the vinylogous lactam **13**, a compound we have not been able to isolate from the reaction mixture. Another possible pathway to compounds **5** and **6** involves the direct [3,5]-sigmatropic rearrangement of imine **8** and aldehyde **9** to give tetraenes **12** and **6**, respectively. Theoretical studies by Houk and co-workers[6] on the [3,5]-sigmatropic reaction of the parent all-carbon system suggest that diradical intermediates are likely to be involved. Studies by Kohmoto et al.[7] also indicate that this type of reaction can occur within the norcaradiene framework. Our own calculations (see below) suggest that a [3,5]-sigmatropic process is probably operating during the course of the transformations described herein.

Interestingly, the conversion of **9** into **6** proposed above seems to occur in a reversible manner. Thus, when a pure sample of compound **6** was resubjected to reaction with DIBAl-H in CH_2Cl_2 at −40 °C (Scheme 2) and the reaction mixture quenched with aqueous HCl, then alcohol **4** was obtained in 66% yield. Similarly, oxidation of compound **4** with pyridinium chlorochromate (PCC)[8] in CH_2Cl_2 at 18 °C for 2 hours regenerated, presumably via the initially formed aldehyde **9**, the fenestratetraene **6** in 76% yield (based on recovered starting material). In contrast, when the readily obtained PTAD adduct, **14** (76% yield), of alcohol **4** was oxidized with PCC then the stable aldehyde **15** was obtained in 88% yield. Attempts to effect the DIBAl-H-mediated reduction of the readily obtained PTAD adduct, **16** (87% yield), of nitrile **3** failed, presumably because of competing reactions involving the carbonyl-containing residues within the former compound.

In a further attempt to probe the nature of the conversion of **9** into **6**, the dihydro form of the former compound was sought on the basis that it could undergo a [3,3]- but not a [3,5]-sigmatropic rearrangement reaction. To these ends, compound **4** was subjected to reaction with dihydrogen in the presence of palladium on carbon (Scheme 3) and the desired diene **17** thereby obtained, albeit in low yield (14%) because of the competing formation of over-reduced and isomeric materials.[2] Upon treatment of compound **17** with PCC or the Ley–Griffith reagent—tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO)[9]—a product containing a newly incorporated oxygen atom (in the form of a ketone) was obtained. On the basis of the spectroscopic data, we believe alcohol **17** is initially converted into aldehyde **18** (the sought-after dihydro form of aldehyde **9**) and that this itself undergoes an allylic oxidation to give enone **19**.[10] Finally, compound **19** engages in a [3,3]-sigmatropic rearrangement to give the observed product **20** (61%), which itself is a fenestrane.



Scheme 3. The synthesis and oxidative rearrangement of [4.3.1]propellenol **17**.

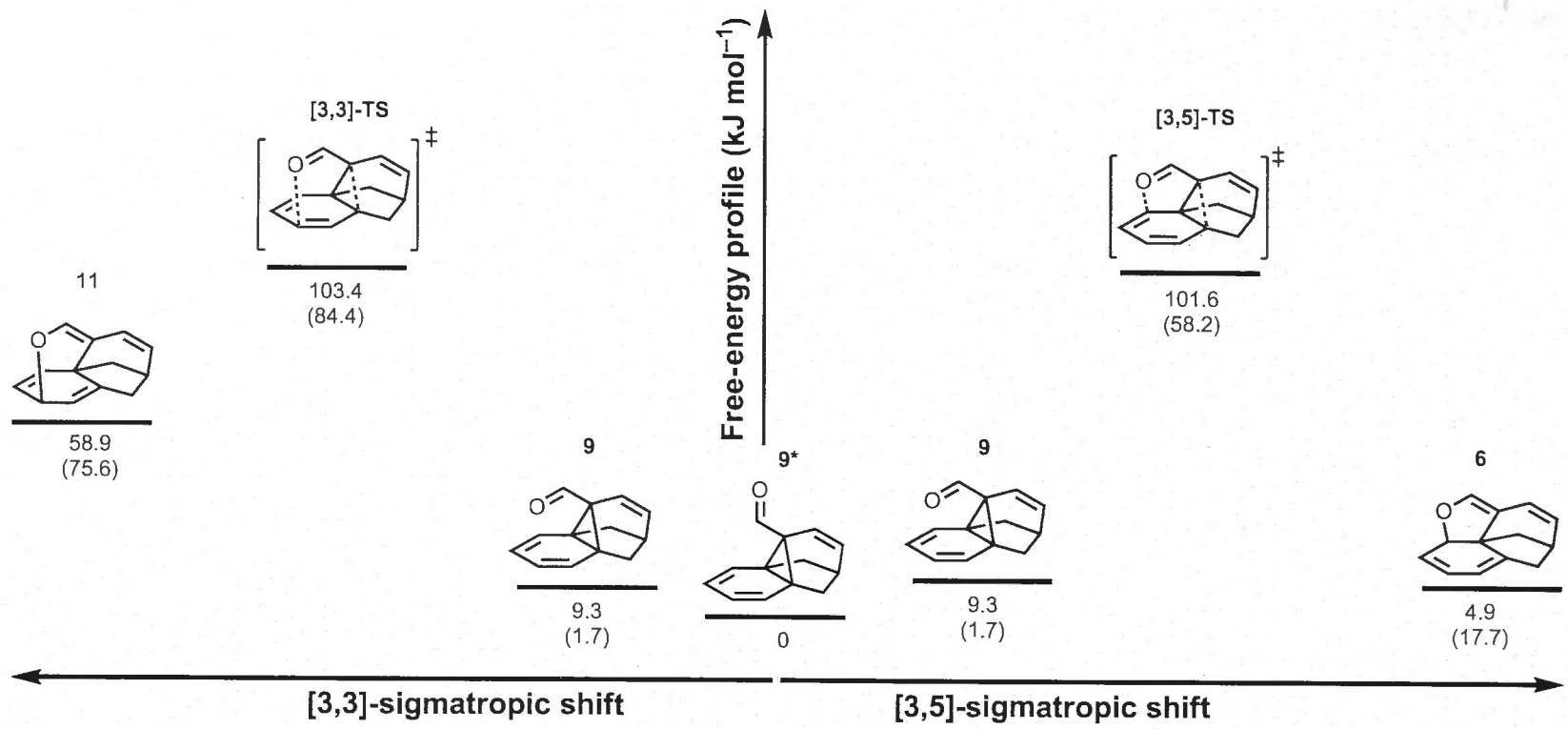


Figure 3. Gibbs-free-energy profiles for the [3,5]- and [3,3]-sigmatropic rearrangements of [4.3.1]propelladiene **9** in which the OTf group is replaced with a hydrogen atom (the values in parentheses refer to Me_2HAl-complexed analogues whereas * denotes the lowest energy conformer of **9**).

Because the above-mentioned experiments failed to differentiate between the two possible reaction pathways shown in Scheme 1, namely between a direct [3,5]-sigmatropic rearrangement and a [3,3]-sigmatropic rearrangement followed by a 1,3-migration process, computational assessments of the energetics of the interconversion of aldehyde **9** and fenestratetraene **6** were carried out. These were conducted at a high level of theory [G3(MP2)RAD(+) and under "conditions" reflecting the experimental ones][11] albeit on compounds in which the OTf group was replaced by a hydrogen atom. These computations (Figure 3) revealed that the ground state energies of the two compounds were comparable (9.3 kJ mol^{-1} versus 4.9 kJ mol^{-1}) whereas that of compound **11** was considerably higher (58.9 kJ mol^{-1}). A qualitatively similar situation was observed for the Me_2HAl-complexed forms of compounds **6** and **11**, namely the complex of **11** was also of higher energy than that of aldehyde **9**. It should be stressed that while the calculations presented here indicate that the equilibrium lies in favor of compound **9** (with **6** being 4.9 kJ mol^{-1} higher in energy), this is entirely due to the model chosen where the OTf group was replaced with a hydrogen atom to reduce the computational cost. Qualitative assessment at a lower level of theory [B3LYP/6-31+G(d)] revealed that inclusion of the OTf group leads to compound **6** being the predominant (thermodynamically more stable) product, an outcome that is consistent with the experimental findings.

The transition states for the conversion of **9** into **6** and the conversion of **9** into **11** were calculated to be of similar energies (101.6 kJ mol^{-1} versus 103.4 kJ mol^{-1}) but very significant differences were encountered for the corresponding Me_2HAl-complexed compounds (58.2 kJ mol^{-1} versus 84.4 kJ mol^{-1}). The calculated natural-bond-order (NBO) atomic charges and solvation free energies indicate a significantly more polarized transition state in which, for example, the atomic charge on the carbonyl oxygen is 0.024 *e* more negative. These characteristics might account for the different stabilities of the Me_2HAl-complexed transition states.

The transition states detected were all closed-shell singlets and various attempts to locate either singlet biradical transition states or intermediates were unsuccessful. This result is unexpected because the [3,5]-sigmatropic rearrangement is thermally disallowed and when it does occur, it is thought to proceed through a stepwise pathway involving biradical intermediates.[6] Inspection of the frontier molecular orbitals (Figure 4) appears to provide an explanation in that the molecular geometry facilitates overlap between the HOMO (the π orbital of the diene) and the π^* orbital of the carbonyl group (CO π^*). This overlap results in an activation barrier of approximately 100 kJ mol^{-1}. This is relatively low in comparison to the values that are typical for thermally allowed hydrocarbon-based pericyclic reactions, which have activation barriers of approximately 140 kJ mol^{-1}.[6]

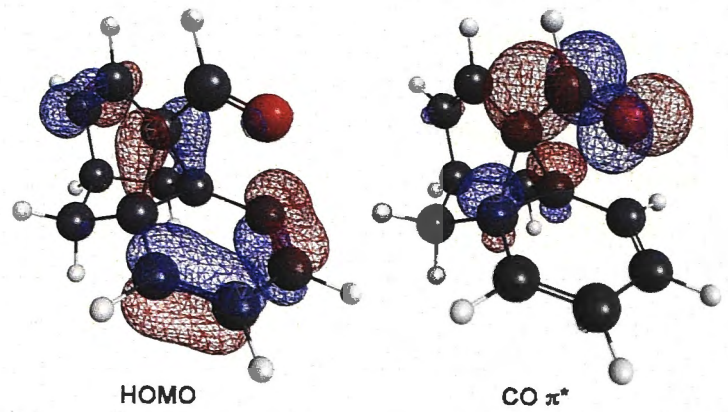


Figure 4. Frontier molecular orbitals of intermediate **9** (see Scheme 1) obtained at the B3LYP/6-31G(d) level of theory.

Under the "reaction conditions" used in the computational work (−40 °C), the calculated barriers associated with direct conversion of both **9** into **6** and **9** into **11** translate

into half-lives of greater than 260 years. By comparison, the corresponding barriers associated with the Me_2HAl-complexed compounds confer half-lives that are consistent with the time-scale of the actual experiments. On this basis, acid-catalyzed [3,5]-sigmatropic rearrangements are believed to be operative in the conversions of **3** into **6**, **4** into **6**,[12] and **6** into **4**.

The above-mentioned transformations represent new and unconventional means of generating fenestranes and suggest that oxa- and aza-based variants of the [3,5]-sigmatropic rearrangement could be used for assembling complex heterocyclic frameworks. In light of these results, it is conceivable that the "retro-Claisen" rearrangement product observed during the course of the recently reported total synthesis of salvileucalin B (**1**)[13] may result from the operation of a [3,5]-sigmatropic rather than a [3,3]-sigmatropic process.

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Keywords: cleavage reactions · fenestratetraenes · norcaradienes · salvileucalin B · sigmatropic rearrangement

[1] Y. Aoyagi, A. Yamazaki, C. Nakatsugawa, H. Fukaya, K. Takeya, S. Kawauchi, H. Izumi, *Org. Lett.* **2008**, *10*, 4429.
[2] N. Heinrich, M. G. Banwell, A. C. Willis, I. A. Cade, R. J. Capon, X.-C. Huang, *Aust. J. Chem.*, in press.
[3] For useful points of entry into the literature on fenestranes, see: a) M. Charpenay, A. Boudhar, G. Blond, J. Suffert, *Angew. Chem.* **2012**, *124*, 4455; *Angew. Chem. Int. Ed.* **2012**, *51*, 4379, and references cited therein; b) S. E. Denmark, J. I. Montgomery, L. A. Kramps, *J. Am. Chem. Soc.* **2006**, *128*, 11620, and references cited therein; c) R. Keese, *Chem. Rev.* **2006**, *106*, 4787; d) H. Hopf, *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim, **2000**, pp. 88–94.
[4] R. C. Cookson, S. S. Gupte, I. D. R. Stevens, C. T. Watts, *Org. Synth.* **1971**, *51*, 121.
[5] Crystallographic data for compound **5**: $C_{15}H_{11}F_6NO_5S_2$, $M=463.38$, $T=200$ K, triclinic, space group $P\bar{1}$, $Z=2$, $a=6.8778(2)$, $b=10.8844(4)$, $c=12.8790(4)$ Å, $\alpha=99.1558(19)°$, $\beta=102.708(2)°$, $\gamma=104.325(2)°$; $V=887.71(5)$ Å^3, $D_x=1.733$ g cm^{-3}, 4063 unique data ($2\theta_{max}=55.2°$), $R=0.051$ [for 3003 reflections with $I>2.0\sigma(I)$]; $Rw=0.132$ (all data), $S=0.95$. Crystallographic data for compound **7**: $C_{22}H_{16}F_3N_3O_6S$, $M=507.45$, $T=200$ K, triclinic, space group $P\bar{1}$, $Z=2$, $a=6.6517(2)$, $b=11.4024(6)$, $c=14.7561(8)$ Å, $\alpha=79.894(2)°$, $\beta=83.096(3)°$, $\gamma=78.323(3)°$; $V=1074.84(9)$ Å^3, $D_x=1.568$ g cm^{-3}, 4921 unique data ($2\theta_{max}=55°$), $R=0.060$ [for 3027 reflections with $I>2.0\sigma(I)$]; $Rw=0.153$ (all data), $S=0.97$. CCDC-891377 (**5**) and 891378 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
[6] A. G. Leach, S. Catak, K. N. Houk, *Chem. Eur. J.* **2002**, *8*, 1290.
[7] S. Kohmoto, N. Nakayama, J.-i. Takami, K. Kishikawa, M. Yamamoto, K. Yamada, *Tetrahedron Lett.* **1996**, *37*, 7761, and references cited therein.
[8] E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, *16*, 2647.
[9] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.
[10] The possibility that the allylic oxidation step takes place first cannot be discounted.
[11] Gas phase Gibbs free energies were calculated with G3(MP2)-RAD(+)//B3LYP/6-31+G[d]. Solvation free energies were calculated using the SMD model at the M06–2X/6-31+G(d,p) level of theory in CH_2Cl_2 on solution-phase optimized geometry; the solvation contribution to the reaction energies (at 233 K) was approximated from those obtained at 298 K.
[12] In the case of this rearrangement, we assume the acidic nature of the reaction medium resulting from the presence of PCC facilitates the conversion of aldehyde **9** into oxa-[5.6.5.6]fenestratetraene **6**.
[13] S. Levin, R. R. Nani, S. E. Reisman, *J. Am. Chem. Soc.* **2011**, *133*, 774.

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